CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208032Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 208032	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Kovanaze Established/Proper Name: Tetracaine HCl & Oxymetazoline HCl Dosage Form: nasal spray Strengths: 6 mg tetracaine HCl and 0.1 mg oxymetazoline HCl in each 0.2 mL spray. (b) (4) .		
Applicant: St. Renatus		
Date of Receipt: May 29, 2015		
PDUFA Goal Date: March 29, 2016; June 29, 2016 due to clock extension	Action Goal Date (if different): June 29, 2016	
RPM: Mavis Darkwah, PharmD		
Proposed Indication(s): regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
OTC nasal decongestant monograph (21 CFR Part 341) □	No specific nonclinical data are present in the monograph; however, the monograph represents an Agency finding of safety and efficacy which reduced the amount of nonclinical data necessary for approval. Specifically, the Agency finding was used in lieu of the full battery of pharmacology and toxicology studies normally required if this were a b1 application. Specific sections of proposed package insert:5.6 Monoamine Oxidase Inhibitors and DRUG INTERACTIONS
Published literature	Nonclinical data: The Sponsor submitted copies of published literature discussing the pharmacology and toxicology of the active ingredients. These were reviewed to determine if there were any additional findings of toxicity that would impact the product labeling. They do not appear to impact the labeling with the exception of some pharmacology data on oxymetazoline. Specific clinical sections of the proposed package insert rely on published literature: WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

The Applicant stated that they are also relying on the nonclinical safety findings of OTC monograph for nasal decongestant products (21 CFR Part 341), as support for a 505(b)(2) application with respect to oxymetazoline hydrochloride component in Kovanaze.

The applicant relies on the oxymetazoline monograph for language in 5.6 Monoamine Oxidase Inhibitors and DRUG INTERACTIONS. The proposed product and the oxymetazoline monograph have the same route of administration and similar doses. Therefore, reliance on the warning language "Risk of Hypertension with Concomitant Use of Oxymetazoline and Monoamine Oxidase Inhibitors" applies to the drug substance oxymetazoline itself regardless of product formulation so it also applies to this product.

The scientific bridge for the nonclinical data is based on the fact that the toxicology studies use the same chemical compound, which is independent of the drug product formulation. The results are compared based on a body surface area comparison when actual exposure data are not available. When exposure data are available, the data are used to put the findings into perspective.

For the WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS sections of the proposed package insert, the applicant relies upon extrapolation of safety information in the oxymetazoline monograph and data from published literature to Kovanaze. The data from the published literature and the monograph are directly relevant to this drug product as the findings are based on exposure to the drug substance and are independent of the drug product formulation.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(Afrin, Dristan·® Long Lasting, and pontocaine are discussed, but I do not consider them to be "listed" drugs)

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☒

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: Synera (Right of reference provided)

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph: oxymetazoline

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").
Kovanaze is a combination of oxymetazoline and tetracaine to be administered intranasally.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

All patents on Synera appear to have expired

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

MAVIS Y DARKWAH
06/29/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 29, 2016
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208032
Product Name and Strength:	Kovanaze (tetracaine HCl and oxymetazoline HCl) Nasal Spray 6 mg/0.1 mg per 0.2 mL spray
Submission Date:	June 29, 2016
Applicant/Sponsor Name:	St. Renatus, LLC
OSE RCM #:	2015-1589-2
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products requested that we review the revised carton labeling and Instructions for Use (IFU) for Kovanaze (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memorandum.[1]

2 CONCLUSION

The revised carton labeling and Instructions for Use (IFU) for Kovanaze are acceptable from a medication error perspective. We have no further recommendations at this time.

[1] Schlick J. Label and Labeling Review Memorandum for Kovanaze (NDA 208032). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JUN 27. 9p. OSE RCM No.: 2015-1589-1.

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/s/

JAMES H SCHLICK
06/29/2016

BRENDA V BORDERS-HEMPHILL
06/29/2016

MEMORANDUM

REVIEW OF PROPRIETARY NAME

Division of Medication Error Prevention and Analysis (DMEPA) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 28, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208032
Product Name and Strength:	Kovanaze (tetracaine HCl and Oxymetazoline HCl) Nasal Spray 6 mg/0.1 mg per 0.2 mL spray
Submission Date:	June 23, 2016
Applicant/Sponsor Name:	St. Renatus, LLC
OSE RCM #:	2015-722507-1
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

This memorandum is to re-assess the proposed proprietary name, Kovanaze, based on the revised strength. The proposed name, Kovanaze, was found acceptable in OSE review# 2015-722507 dated August 6, 2015[1] and OSE review #2014-17224 dated September 2, 2014.[2] The established name of the product was originally presented as (b) (4) Based on the recommendation by the Office of Pharmaceutical Quality, St. Renatus revised the strength of the product to reflect the strength in milligrams of the hydrochloride salts.

[1] Shah, M. Proprietary Name Review for Kovanaze (NDA 208032). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 06. 68 p. OSE RCM No.: 2015-722507.

[2] Schlick J. Proprietary Name Review for Kovanaze (IND 070868). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 SEP 02. 25 p. OSE RCM No.: 2014-17224.

2 METHODS AND MATERIALS REVIEWED

For reassessment of the proposed proprietary name, we evaluated previous proprietary name reviews dated August 6, 2015 and September 2, 2014 to assess whether the change in strength would alter our previous conclusion regarding the acceptability of the proposed proprietary name. We searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates.[3] Our search did not identify any USAN stems present in the proprietary name.

We evaluated the results of our previous POCA search in OSE review #2015-722507[4] to identify names with overlapping strength and/or dose with the new 6 mg/0.1 mg per 0.2 mL strength. Our search did not identify any names with an overlap in strength and/or dose with the 6 mg/0.1 mg per 0.2 mL strength.

Our USAN stem search and evaluation of previous POCA search results did not identify any new names that represent a potential source of drug name confusion. Our evaluation has not altered our previous conclusion regarding the acceptability of the proposed proprietary name. As a result, we maintain that the name is acceptable.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have further questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

[3] USAN stem search conducted on June 27, 2016.

[4] POCA search conducted on June 25, 2015.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

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/s/

JAMES H SCHLICK
06/28/2016

BRENDA V BORDERS-HEMPHILL
06/28/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 27, 2016
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208032
Product Name and Strength:	Kovanaze (tetracaine HCl and oxymetazoline HCl) Nasal Spray 6 mg/0.01 mg per 0.2 mL spray
Submission Date:	June 23, 2016
Applicant/Sponsor Name:	St. Renatus, LLC
OSE RCM #:	2015-1589-1
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels, carton labeling, and Instructions for Use (IFU) for Kovanaze (tetracaine HCl and oxymetazoline HCl) Nasal Spray (Appendix A) to determine if it is acceptable from a medication error perspective. The recommendations in our original review were not sent to the Sponsor because the dose cohorts were reduced from four to two, requiring revisions to the packaging and IFU. St. Renatus has resubmitted their packaging and IFU reflecting the new dose cohort information, and we reviewed these changes.[1]

2 OVERALL ASSESSMENT AND CONCLUSION

[1] Schlick J. Human Factors, Label and Labeling Review for Kovanaze (NDA 208032). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 NOV 19. 29 p. OSE RCM No.: 2015-1589.

St. Renatus revised the pediatric dose cohorts to include only patients [redacted] who weigh 40 kg or more to receive 2 sprays (0.2 mL per spray); the adult dosing remained the same [2 sprays (0.2 mL per spray)]. Thus, eliminating the need for a [redacted]. The IFU validated in the HF validation study conducted in March 2015 (submitted May 29, 2015) and found acceptable used an IFU that included instructions for [redacted] adult doses [redacted] IFU. The IFU submitted on June 23, 2016 via email (See Appendix A) was revised to [redacted] be consistent with the prescribing information. We reviewed the revised IFU and compared these revisions to the IFU used in the adult validation study. We determined the results of the adult validation study are still relevant to the revised IFU and will not require further validation testing. We have some additional recommendations to convey to St. Renatus to improve the clarity of the IFU. These recommendations, if implemented, will not require further validation testing as well.

Additionally, in emails dated 23 and 27June16, OPQ determined that based on exception rules and a prior agreement with the Agency, the drug product will use the salt name as the established name and should include "HCl" but that the strength is to be expressed in mg/mL instead of %. We considered label requirements set forth in 21 CFR 201.10(i) and determined that the container label has the required information (Appendix A).

We also have an additional recommendation to increase the prominence of the storage statement for the carton labeling and outer shipping box label. Our recommendations are provided in Section 3.

3 RECOMMENDATIONS FOR ST. RENATUS

We recommend the following be implemented prior to approval of this NDA:

A. Instructions for Use

1. As a reference to dental professionals, add brief dosing instructions in table format at the beginning of the IFU, (i.e., 2 sprays with an optional third dose for adults, and 2 sprays for children [redacted] who weigh 40 kg or more). This information is a helpful reference to dental professionals, and the addition of this information would not require further validation testing.

2. Revise the following statements in the instructions for the spray positions located just before step 1a from "Spray Position 1 (Approximately Horizontal)…" and Spray Position 2 (Approximately 45 Degree Angle)…" to read "Spray Position for First Spray (Approximately Horizontal)…" and "Spray position for second spray (Approximately 45 Degree Angle)…" This revision may provide clarity for dental professionals and would not require further validation testing.

B. Carton Labeling and Outer Shipping Box Labeling

1. Revise the storage statement and bold it as follows: "**Must be refrigerated, store at 2°C to 8°C (36°C to 46°F)**". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

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/s/

JAMES H SCHLICK
06/27/2016

BRENDA V BORDERS-HEMPHILL
06/27/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 24, 2016

To: Mavis Darkwah, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 208032
KOVANAZE (tetracaine and oxymetazoline) Nasal Spray
Professional Labeling Review (Addendum to June 8, 2016 Review)

As requested in DAAAP's consult dated July 14, 2015, OPDP has reviewed the substantially complete prescribing information and container and carton labeling for KOVANAZE (tetracaine and oxymetazoline) Nasal Spray. The substantially complete prescribing information was provided to OPDP on June 23, 2016, via email by Mavis Darkwah with the file name "\\fdsfs01\ODE2\DAAAP\NDA and sNDA\NDA 208032 (tetracaine and oxymetazoline St Renatus)\Labeling\Current Labeling\Carton container\Revised 23June2016".

OPDP has provided comments on the substantially complete prescribing information and instruction for use labeling in the attached documents below.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

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KOUNG U LEE
06/24/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 8, 2016

To: Mavis Darkwah, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 208032
KOVANAZE (tetracaine and oxymetazoline) Nasal Spray
Professional Labeling Review

As requested in DAAAP's consult dated July 14, 2015, OPDP has reviewed the substantially complete prescribing information and container and carton labeling for KOVANAZE (tetracaine and oxymetazoline) Nasal Spray. The substantially complete prescribing information was provided to OPDP on May 31, 2016, via email by Mavis Darkwah with the file name "kovanaze-pi-201505.docx".

OPDP has provided comments on the substantially complete prescribing information, container, carton, and (b) (4) labeling in the attached documents below. .

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

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/s/

KOUNG U LEE
06/08/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 05-26-2016

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia, and Addiction Products

Drugs: Kovanaze (Tetracaine HCl % and oxymetazoline HCl) nasal spray
NDA 208032

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Labeling as part of 505(b)(2) NDA

Applicant: St. Renatus, LLC

Materials Reviewed:
- Applicant's proposed labeling
- Literature review

Consult Question: Please advise regarding Pregnancy and Lactation Labeling Rule (PLLR) Labeling

INTRODUCTION

The applicant submitted a 505 (b)(2) application for Kovanaze (Tetracaine HCl 3% and oxymetazoline HCl 0.05%) nasal spray on May 29, 2015, and included labeling in the format of the Pregnancy and Lactation Labeling Rule (PLLR). The proposed indication is for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J in adults and pediatric patients weighing 40 kg or more. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 14, 2015, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Kovanaze nasal spray contains tetracaine HCl 3%, a local anesthetic, and oxymetazoline HCl 0.05%, an alpha-adrenergic agonist local vasoconstrictor. Tetracaine has been on the market since 1936 and oxymetazoline was initially approved in 1964. Local anesthetics are administered with a local vasoconstrictor to allow the local anesthetic to remain at the target site for a sufficient time to complete the dental procedure (see Dental Officer review by Dr. Fred Hyman in DARRTS).[1] Kovanaze is supplied in a single-use delivery system. The reference listed drug is Synera (lidocaine and tetracaine topical patch) for the tetracaine component. The applicant is relying on reference to the OTC monograph for nasal decongestant products (21 CFR Part 341) as it applies to the findings of nonclinical safety of oxymetazoline as support for a 505(b)(2) application with respect to oxymetazoline hydrochloride.

Dental Care during Pregnancy

The American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women maintain good oral health to improve the oral health and general health of the woman and to reduce the transmission of potentially caries-producing oral bacteria to their infants.[2] In a Committee Opinion, ACOG states that although some studies have shown a possible association between periodontal infection and preterm birth, evidence has failed to show any improvement in outcomes after dental treatment during pregnancy. Available studies did not raise any concern about the safety of dental services during pregnancy. ACOG states that local anesthesia, including administration with local vasoconstriction, is safe in pregnancy, and that conditions that require immediate treatment, such as extractions, root canals, and restoration of untreated caries, may be managed at any time during pregnancy. This assessment is based on published data for local lidocaine and epinephrine injection. Lidocaine was not associated with malformations in 293 first trimester exposed pregnancies in the Collaborative Perinatal Project.[3]

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[1] Review in DARRTS 3-12-2016

[2] American College of Obstetricians and Gynecologists Oral Health Care During Pregnancy and Through the Lifespan Committee Opinion Number 569. August 2013 (Reaffirmed in 2015).

[3] Heinonen OP, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. Littleton, Massachusetts: Publishing Sciences Group, Inc., pp 358, 360, 1977.

Since the publication of the ACOG Committee Opinion in 2013, there has been a new publication on a prospective cohort study conducted in Israel that followed 210 pregnant women exposed to dental local anesthetics (112 were exposed in the first trimester) and compared them with 794 women not exposed to teratogens. There was no difference in the rate of major malformations.[4] Information on individual drugs is not provided, however the authors comment that the most commonly used local anesthetic in the U.S. and Israel is lidocaine with epinephrine.

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR), took effect.[5] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW OF DATA

Review of Published Data

Applicant's review

The applicant reviewed the published literature and proposed the inclusion in labeling of human data from a retrospective study in pregnant women exposed to nasal oxymetazoline that showed no significant relationship between exposure to decongestants and major congenital malformations.[6] Subjects registering for prenatal care at San Diego Kaiser-Permanente Health Care Plan between June 1978 and December 1989 were asked to complete a questionnaire regarding their history of asthma or symptoms of asthma. All subjects with asthma were recruited to enter the study, and control subjects without asthma who matched a previously entered subject with asthma on the basis of age, parity, and smoking (> 10 cigarettes/day for > 1 month of pregnancy) were also recruited. All medications used since conception were recorded. There were 321 women exposed to decongestants in the first trimester (includes 197 women exposed to nasal oxymetazoline) who were compared to 1,175 unexposed women. There was no statistically significant difference in major malformations between the exposed and unexposed group. No statistical analysis was performed for individual drugs.

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[4] Hagai a, Diav-Citrin O, et al. Pregnancy outcome after in utero exposure to local anesthetics as part of dental treatment. J of the American Dental Association 2015:146(8):572-580.

[5] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

[6] Schatz M, Zeiger RS, Harden K et al. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 1997;100: 301-306.

An association with maternal use of decongestants (including oxymetazoline) and gastroschisis was reported in a case-control study of 110 infants with gastroschisis[7], although the finding was not statistically significant (odds ratio 2.4, 95% confidence interval 1.0-5.4). The maternal use of the decongestants phenylpropanolamine and pseudoephedrine appeared to account for the association, and there was no separate analysis of oxymetazoline (the number of cases exposed to oxymetazoline is not stated).

In one case report, the excessive use of oxymetazoline nasal spray (2 doses in each nostril half an hour prior to and 5 doses in the 16 hours prior to a nonstress test) by a woman in her 41st week of pregnancy was associated with a nonreactive nonstress test and late fetal decelerations, suggesting that uterine perfusion might have been impaired.[8]

Published data not reviewed by the applicant:
Nasal oxymetazoline
A case-control study using data from the Slone Epidemiology Center Birth Defects Study assessed use of oral and nasal decongestants during pregnancy and the risk of birth defects. This study did not find an association between use of nasal oxymetazoline during the first trimester and ventricular septal defect (VSD) (based on 8 exposed cases), pyloric stenosis (based on 5 exposed cases), and cleft lip with or without cleft palate in the offspring (based on 6 exposed cases).[9] An association with maternal use of nasal oxymetazoline in the second trimester and renal collecting systems anomalies was seen (OR=3.1, 95% CI:1.3, 6.9), based on 10 exposed cases.[10] The authors comment that the association between second trimester use of nasal oxymetazoline and renal collecting system anomalies should be interpreted with caution as this finding was one of several findings that occurred in additional exploratory analyses that were designed to generate hypotheses. Due to the multiple comparisons that were performed, the associations that were seen may have been due to chance.

The frequency of congenital anomalies was no greater than expected among the infants of more than 250 women who used oxymetazoline during the first trimester of pregnancy in two retrospective cohorts of the Boston Collaborative Drug Surveillance Program.[11,12]

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[7] Torfs CP, Katz EA, Bateson TF et al: Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology 54:84-92, 1996.

[8] Baxi LV et al: Fetal heart rate changes following maternal administration of a nasal decongestant. Am J Obstet Gynecol 153:799-800, 1985.

[9] Yau W-P, Mitchell AA, Lin KJ, Werler MM, Hernandez-Diaz S. Use of decongestants during pregnancy and the risk of birth defects. Am J Epidemiol 2013;178(2):198-208.

[10] Web material (table 3).

[11] Jick H, Holmes LB, Hunter JR, Madsen S, Stergachis A: First-trimester drug use and congenital disorders. JAMA 246:343-346, 1981.

[12] Aselton P, Jick H, Milunsky A, Hunter JR, Stergachis A: First trimester drug use and congenital disorders. Obstet Gynecol 65(4):451-455, 1985.

When a single dose of 0.05% oxymetazoline nasal spray was studied in 12 uncomplicated pregnancies in the third trimester of pregnancy, there was no significant change in blood flow velocity in the uterine arcuate artery, fetal aorta, or umbilical artery.[13]

Table 1. Summary of Published Data on Nasal Oxymetazoline Exposure In Pregnancy

Author	Study Design	N exposed	N unexposed	Findings	Comments
Schatz 1997	retrospective cohort	197	1,175	-no statistically significant difference between use of decongestants and major malformations	*-No statistical analysis was performed for individual drugs.*
Torfs 1996	Case control	Number of oxymetazoline exposures not indicated; 110 infants with gatroschisis; 220 controls without a birth defect		no statistically significant difference between use of decongestants and gastroschisis	*-Number of oxymetazoline exposures is not known* *-No statistical analysis was performed for individual drugs.*
Yau 2013	Case control	34 exposed cases in the first trimester;10 exposed cases in the second trimester; 66 exposed controls without a birth defect		-no statistically significant difference in: VSD, pyloric stenosis, cleft lip with or without palate - An association with maternal use of oxymetazoline in the second trimester and renal collecting	*-small number of exposed cases*

[13] Rayburn WF, Anderson JC, Smith CV, Appel LL, Davis SA: Uterine and fetal Doppler flow changes from a single dose of a long-acting intranasal decongestant. Obstet Gynecol 76:180-2, 1990.

				systems anomalies was seen (OR=3.1, 95% CI:1.3, 6.9).	
Jick 1981	retrospective database review	100-199 (approximate number)	0	"no strong association with congenital disorders"	*Exact number of oxymetazoline exposures is not known -No statistical analysis was performed*
Aselton 1985	retrospective database review	155 exposed	0	"no strong association with congenital disorders"	*No statistical analysis was performed*

Reviewer comments
All of the published studies except for one study (Yau, 2013), were done 20-35 years ago and have methodologic issues. For example, the studies include the following limitations:

- *Exposure to oxymetazoline was combined with other decongestants such as pseudoephedrine, and there is no assessment of oxymetazoline exposure alone*
- *There are no pre-specified statistical analyses for birth defect prevalence*
- *The number of pregnant women exposed to oxymetazoline are imprecise or unknown*
- *There are no comparator groups/cohorts.*

In addition, these studies are based on oxymetazoline used as a nasal decongestant, and not as a single dose administered for a dental procedure. There is no information on dose and duration of use. Use of nasal decongestants probably involves repeat dosing over several days and it is not clear if the data are applicable to a single dose of Kovanaze.

Available data do not indicate a safety concern except for one study (Yau, 2013) that showed an association with maternal use of oxymetazoline in the second trimester and renal collecting systems anomalies, which the authors comment may have been a chance finding due to multiple comparisons. This finding has not been corroborated in any other study. This study is limited by the small number of exposed cases and recall bias, which is a limitation of case control studies.

Therefore, review of available published epidemiologic studies of nasal oxymetazoline used as a decongestant during pregnancy do not identify a consistent association with any specific malformation or pattern of malformations.

Tetracaine

Tetracaine local anesthesia was not associated with adverse pregnancy outcome in 23 exposed pregnancies in the Collaborative Perinatal Project.[14]

Reviewer comment
These data are limited and therefore it is not possible to draw any conclusions on the safety of tetracaine local anesthesia in pregnancy.

Lactation data
There are no published data on tetracaine or oxymetazoline levels in milk.

Systemic Absorption
The issue of whether there is systemic absorption of tetracaine and oxymetazoline was discussed with clinical pharmacology reviewer Dr. David Lee and at labeling meetings with DAAAP. Based on Dr. Lee's Clinical Pharmacology review, plasma concentrations of tetracaine in all subjects were at or below the limit of assay quantification (0.05 ng/mL).[15] However, tetracaine is rapidly metabolized to p-butylaminobenzoic acid (PBBA), which does not have anesthetic activity. The peak plasma concentration of PBBA occurs within approximately 25 minutes, and the half-life is 2.6 hours. Therefore, although there is no systemic absorption of tetracaine, there is systemic absorption of its metabolite PBBA. The amount of fetal exposure is not known. Oxymetazoline attains maximum concentration within approximately 10 minutes following the end of dosing, and the half-life is 5.2 hours. Therefore, there is systemic absorption of oxymetazoline, and the amount of fetal exposure is not known.

DISCUSSION
Pregnancy
Published epidemiologic studies of nasal oxymetazoline used as a decongestant during pregnancy do not identify a consistent association with any specific malformation or pattern of malformations. Because of the limitations of the data on oxymetazoline exposure in pregnancy, DPMH recommends not describing these data in labeling, but including a summary of the information reviewed and the limitations of the data.

Tetracaine data are limited and it is not possible to draw any conclusions on the safety of tetracaine local anesthesia in pregnancy; therefore, DPMH recommends not including these data in labeling.

Lactation
There are no published data on tetracaine or oxymetazoline levels in milk. DPMH recommends that the following risk/benefit statement be included in subsection 8.2 Pregnancy, under the Risk Summary heading:
The development and health benefits of breastfeeding should be considered along

[14] Heinonen OP, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. Littleton, Massachusetts: Publishing Sciences Group, Inc., pp 358, 360, 1977.

[15] Review in DARRTS 2-22-2016

with the mother's clinical need for Kovanaze and any potential adverse effects on the breastfed infant from Kovanaze or from the underlying maternal condition.

Females and Males of Reproductive Potential
Animal data show infertility effects. DPMH discussed with DAAAP toxicology reviewers whether animal data based on repeat dosing are relevant to the human single dose administration. DAAAP toxicology reviewers' opinion is that the data are clinically relevant and, therefore, they recommend inclusion of this information under subsection 8.3 Females and Males of Reproductive Potential.

CONCLUSION
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of Kovanaze labeling were structured to be consistent with the PLLR. DPMH has the following recommendations for Kovanaze labeling:

- **8.1 Pregnancy**
  - The "Pregnancy" subsection of Kovanaze labeling was formatted in the PLLR format to include "Risk Summary" and "Data" sections
- **8.2 Lactation**
  - The "Lactation" subsection of Kovanaze labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" sections.
- **8.3 Females and Males of Reproductive Potential**
  - The "Females and Males of Reproductive Potential" subsection of Kovanaze labeling was formatted in the PLLR format to include a statement on infertility effects based on animal data.

DPMH LABELING RECOMMENDATIONS
DPMH discussed our labeling recommendations with DAAAP. DPMH recommendations are below and reflect the discussions with DAAAP. **See final labeling for all of the labeling revisions negotiated with the applicant.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on tetracaine use in pregnant women are not sufficient to inform any risks. Published epidemiologic studies of nasal oxymetazoline used as a decongestant during pregnancy do not identify a consistent association with any specific malformation or pattern of malformations *[see Data]*. In animal reproduction and development studies, oxymetazoline given subcutaneously to rats during the period of organogenesis caused structural abnormalities at a dose approximately 7.6 times the level of oxymetazoline (0.3 mg) from the maximum recommended human dose (MRHD) of KOVANAZE. In a pre- and post-natal development study, oxymetazoline given subcutaneously to rats caused embryofetal toxicity manifested by reduced implantation sites and live litter sizes at doses approximately 1.5 times the MRHD level and greater (b) (4) increased pup mortality (b) (4) at (b) (4)

[redacted] times the MRHD level. [redacted] no adverse developmental effects were observed [redacted] subcutaneous [redacted] *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Published epidemiologic studies of nasal oxymetazoline used as a decongestant during pregnancy do not identify a consistent association with any specific malformation or pattern of malformations. These data are limited by the small number of cases exposed, multiple comparisons which may have resulted in chance findings, and analyses based on decongestants as a group.

Animal Data

In an embryofetal development study, pregnant rats [redacted] were administered subcutaneous doses of oxymetazoline at 0.1 mg/kg (7.6 times the [redacted] oxymetazoline from the maximum recommended human dose (MHRD) of KOVANAZE [redacted] tetracaine only at 7.5 mg/kg (3 [redacted] times the [redacted] the MHRD as measured by PBBA [major tetracaine metabolite] AUC [redacted] and oxymetazoline at 0.01, 0.03, and 0.1 mg/kg/day [redacted] in combination with 7.5 mg/kg tetracaine during the period of organogenesis (Gestational Days [GD] 7-17). Treatment with only oxymetazoline at 0.1 mg/kg caused structural abnormalities including external and skeletal malformations (e.g., short forelimb digits, fused arches in thoracic vertebrae, fused ribs, and irregular number of ribs), and variations (e.g., irregularly shaped arches and increased bifid centra in thoracic vertebrae, and un-ossified forelimb phalanx) in the absence of maternal toxicity. [redacted] were not observed when pregnant rats were co-administered oxymetazoline [redacted] with 7.5 mg/kg tetracaine. The no-observed-adverse-effect-level (NOAEL) for fetal [redacted] is 0.03 mg/kg oxymetazoline [redacted] 7.5 mg/kg tetracaine.

In other embryofetal development studies, tetracaine alone administered subcutaneously did not cause structural abnormalities in rats at doses up to 10 mg/kg/day (approximately [redacted] times the MRHD level by body surface area (BSA) comparison) or in rabbits at subcutaneous doses up to 5 mg/kg/day (approximately [redacted] times the MRHD level by BSA comparison).

In a prenatal and postnatal development study, pregnant rats [redacted] were given subcutaneous doses of oxymetazoline only at 0.1 mg/kg ([redacted] times the MHRD level by AUC [redacted] tetracaine only at 7.5 mg/kg (12 times MHRD level by PBBA AUC [redacted] and oxymetazoline at 0.01, 0.03, and 0.1 mg/kg [redacted] in combination with 7.5 mg/kg tetracaine from GD 7 to Lactation Day [LD] 20 (corresponding to the beginning of organogenesis through parturition and subsequent pup weaning). Oxymetazoline treatment decreased the mean number of implant sites/litter at $\geq$ 0.03 mg/kg when administered with 7.5 mg/kg tetracaine (approximately 9%) and without tetracaine administration (5.5%), which resulted in an [redacted] reduction in live litter sizes in these groups. At the end of the lactation period, fetal body weights were significantly

decreased at 0.1 mg/kg oxymetazoline dose when administered alone (19%) and co-administered with 7.5 mg/kg/day tetracaine (11%). In addition, (b) (4) pup (b) (4) was observed at the 0.1/7.5 mg/kg oxymetazoline/tetracaine dose (b) (4)) compared to the control ((b) (4)). Maternal toxicity (decreased body weight and mortality) occurred at doses of 0.1 mg/kg oxymetazoline alone (b) (4). There were no adverse effects on sexual maturation, neurobehavioral, or reproductive function in the offspring at any maternal dose.

8.2 Lactation

Risk Summary

There are no data on the presence of tetracaine, oxymetazoline, or their metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Detectable levels of oxymetazoline, tetracaine and PBBA were found in the milk of lactating rats following subcutaneous administration of oxymetazoline HCl in combination with tetracaine HCl during the period of organogenesis through parturition and subsequent pup weaning *[see Data]*. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kovanaze and any potential adverse effects on the breastfed infant from Kovanaze or from the underlying maternal condition.

Data

In a pre- and post-natal development study, rats were given subcutaneous doses of oxymetazoline at doses of 0.01, 0.03, and 0.1 mg/kg/day (0.6, 1.5, and 7.6 times, respectively, the maximum recommended human dose (MRHD) level by AUC (b) (4)) in combination with 7.5 mg/kg tetracaine (12 times the MRHD level by tetracaine metabolite AUC (b) (4) from Gestational Day [GD] 7 to Lactation Day [LD] 20. Concentrations of oxymetazoline, tetracaine, and PBBA were measured in the milk of lactating rats at approximately 2 hours post dose on LD 15. The concentrations of oxymetazoline were generally dose dependent (2.5, 7.0, and 33.8 ng/mL at 0.01, 0.03, and 0.1 mg/kg, respectively). The concentrations of tetracaine and PBBA were generally similar across all 7.5 mg/kg tetracaine dosing groups regardless of the presence of oxymetazoline (54.2 – 72.9 ng/mL for tetracaine, and 100.5 – 131.2 ng/mL for PBBA).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on animal data, Kovanaze may reduce fertility in females of reproductive potential. It is not known if the effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

Males

Based on animal data, Kovanaze may decrease sperm motility and sperm concentration *[see Nonclinical Toxicology (13.1)]*.

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/s/

LEYLA SAHIN
05/26/2016

TAMARA N JOHNSON
05/26/2016

LYNNE P YAO
05/26/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, Ophthalmic

Date: February 29, 2016 (**Update- April 28, 2016)

To: Mavis Darkwah, Office of New Drugs, WO22-3111
mavis.darkwah@fda.hhs.gov

Matthew Sullivan, Office of New Drugs, WO22-3126
matthew.sullivan@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Mavis Darkwah

Through: For Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH

From: Jamie Kamon-Brancazio, REGO, DMQ, OC, CDRH

Applicant: St. Renatus, LLC
1000 Centre Avenue
Fort Collins, Colorado 80526
No FEI on record

Application # NDA-208032

Consult # ICC1600039

Product Name: Tetracaine HCl 3% and oxymetazoline HCl 0.05% nasal spray

Pre-Approval Inspection: **No**

Documentation Review: Additional Information Required

Final Recommendation: **Approve**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA-208032.

PRODUCT DESCRIPTION

KovanazeTM Nasal Spray is a fixed-combination drug formulation of two active ingredients, 3% tetracaine hydrochloride (HCl) and 0.05% oxymetazoline HCl, performing anesthetic and vasoconstriction functions, respectively, to achieve regional anesthesia when sprayed into the respiratory region of the nasal cavity. It is provided in single-use, prefilled nasal spray systems that deliver 0.2 mL (containing 6 mg tetracaine HCl and 0.1 mg oxymetazoline HCl).

Kovanaze™ is indicated to induce regional anesthesia sufficient to allow completion of a restorative dental procedure on teeth 4-8 or 9-13 and teeth A-E or F-J when present.

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. St. Renatus, LLC
   1000 Centre Avenue
   Fort Collins, Colorado 80526
   No FEI on record

   Responsibility: Applicant

Inspectional History – No inspectional history was found in FACTS or OSAR

Inspection Recommendation:

An inspection is not required because:

- The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part, however, this firm is the applicant and should demonstrate compliance with 21 CFR part 4 through documentation submission.

2. (b) (4)

(b) (4)

Responsibility – Drug product manufacture and storage

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on (b) (4), provided drug coverage and was classified NAI.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

Inspection Recommendation:
An inspection is not required because:

- The firm's recent drug inspection was acceptable.

3. (b) (4)

Responsibility – Drug product manufacture and storage

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on (b) (4), provided drug coverage and was classified VAI.

Inspection Recommendation:
An inspection is not required because:

- The firm's recent drug inspection was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

DOCUMENTATION REVIEW
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20
According to St. Renatus, manufacturing operations for Kovanaze Nasal Spray, including release testing, are performed by contract manufacturers and laboratories, however the firm did not describe the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements).

The information provided by the firm has inadequately addressed the requirements of 21 CFR

820.20.

**Update- April 28, 2016- Jamie Kamon-Brancazio

Provided in the firm's response dated March 10, 2016, St. Renatus has implemented a Quality Manual which outlines the quality policy, management responsibilities, the product manufacturing and distribution operations flow, the quality system and monitoring program. The Head of Quality who reports directly to the CEO of the company is responsible for the oversight and management of the quality system. The firm's procedures include initial qualification of vendors, periodic audits to ensure continued compliance with GMP requirements, management of change control, non-conformances and corrective and preventive actions, and annual product reviews. The firm utilizes the quality systems of is approved vendors to ensure quality risk is not compromised.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm conducted a risk assessment for the finished product delivery system and determined design controls associated with the identified risks including, product protection, performance, safety and compatibility. The firm also provided a list of user needs, product requirements, design input/output, and verified each requirement along with validation of the nasal spray. However, the firm did not provide a description for design and development planning, design review, design transfer, or design changes.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

**Update- April 28, 2016- Jamie Kamon-Brancazio

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm did not provide a summary or description of the procedure for purchasing controls. The procedure should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers. The procedure should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process. The procedure should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use. The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product. The firm should describe how it applied the purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product or provide evidence of the application (i.e. supplier's agreement).

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

**Update- April 28, 2016- Jamie Kamon-Brancazio

According to the firm's response dated March 10 2016, all material/component vendors, contract manufacturing facilities, contract packaging facilities, contract laboratories, service providers and third party logistics vendors will be qualified by St. Renatus prior to commercial product launch. All vendors are assessed and qualified based off of risk. All vendors have quality agreements in place with St. Renatus that ensures St. Renatus will be notified of all changes in advanced including, but not limited to; raw materials, process consumables,

components, packaging materials, labeling, product process, equipment, facilities, utilities, computer systems, specifications and methods.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100
The firm did not provide a summary of its procedure for its Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

**Update- April 28, 2016- Jamie Kamon-Brancazio

Per the firm's response dated March 10 2016, St. Renatus has implemented a non-conformance, Corrective and Preventative Action procedure to ensure identification of deviations, thorough investigation, impact assessment, root cause analysis, immediate corrections, corrective/preventive actions and effectiveness verification. The non-conformance SOP outlines the identification of the non-conformance, investigation, notifications, determination, segregation and/or quarantine of the product and root cause analysis with causal factors. Upon determination of root cause(s) all corrective and/or preventive actions will have a timeline for completion as well as criteria for determining effectiveness.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170
Installation is not required for this combination product.

Servicing, 21 CFR 820.200
Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls
Aside from performing filling at (b) (4), the firm did not provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product occurs.

(b) (4)

Acceptance Activities

The firm provided component specifications for all materials to be used in the final combination device. Control of the target fill quantity (b) (4) . The firm also provided specific acceptance criteria for appearance, Tetracaine HCl Assay, Oxymetazoline HCl Assay, microbial limits, particulate matter, and delivered dose uniformity. The firm did not provided the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the firm's response for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The approvability of application for Tetracaine HCl 3% and oxymetazoline HCl 0.05% nasal spray, NDA-208032, is approvable from the perspective of the applicable Quality System

Requirements. The documentation review of the firm's response for compliance with the Quality System Requirements showed no deficiencies. Additionally, there were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

_____

Jamie Kamon-Brancazio

Prepared: JKamon-Brancazio: 2/29/16 **Updated 4/28/16
Reviewed: VVerna: 3/1/16; 4/29/2016

CTS No.: ICC1600039
NDA-208032

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Inspectional Guidance

Firm to be inspected:

1. (b) (4)
2. (b) (4)

CDRH recommends the inspection under the applicable Medical Device Regulations of (b) (4)
(b) (4)

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Primary Contact

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THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAVIS Y DARKWAH
05/02/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel 301-796-2110
FAX 301-796-9894

Memorandum

DATE: March 12, 2016

FROM: Fred Hyman, D.D.S. M.P.H, Dental Officer, DDDP

THROUGH: David Kettl, M.D., Team Leader, DDDP

TO: Mavis Darkwah, Pharm.D., RPM, for Sharon Hertz, M.D., Director, DAAAP

Cc: Barbara Gould, CPMS, DDDP

SUBJECT: Consult to the Division of Anesthetic Analgesic and Addiction Drug Products
NDA 20-8032:
Sponsor: St. Renatus
Drug: Kovanaze™ nasal spray;
Indication: Regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J.

DDDP Consult #1739

Material Reviewed:

- Phase 3 protocols for NDA 20-8032 (SR 3-02, SR 3-03 and SR 3-04)
- DARRTS: IND 70868 EOP2 Meeting Minutes March 3, 2011
- Published Literature:
  1. Velasco, Ignacio and Soto, Reinaldo *Anterior and middle superior alveolar nerve block for anesthesia of maxillary teeth using conventional syringe* Dent Res J. 2012 Sep-Oct; 9(5): 535–540.

  2. Ciancio, Sebastian et al. *Comparison of three intranasal mists for anesthetizing maxillary teeth in adults: A randomized, double-masked, multicenter phase 3 clinical trial* JADA April, 2016. In press.

  3. Kohli, Kavita. *A survey of local and topical anesthesia use by pediatric dentists in the United States* Pediatric Dentistry – 23:3, 2001

  4. Singh, P *An emphasis on the wide usage and important role of local anesthesia in dentistry: A strategic review* Dental Research Journal Mar 2012 Vol 9 Issue 2

Introduction and Regulatory Background

There are many approved local anesthetic drugs that are indicated for use prior to dental procedures. The delivery for most of these drugs is by penetration of a needle through the buccal mucosa. Kovanaze Nasal Spray™ (3% tetracaine HCl/0.05% oxymetazoline HCl), the subject of this consultative review, is formulated as a solution that is delivered by spraying premeasured amounts into the nasal cavity. The sponsor posits that the spray diffuses through the sinus and reaches the two nerves that innervate the maxillary anterior and premolar teeth; it is under review for its ability to provide sufficient local anesthesia in that area to allow completion of restorative dental procedures.

The active anesthetic drug substance is tetracaine; oxymetazoline is included as a vasoconstrictor so that the tetracaine remains at the target site for a sufficient time to complete the dental treatment.

The IND for Kovanaze was opened in DAAAP on January 4, 2006. The sponsor conducted phase 1 and phase 2 trials and participated in an EOP2 meeting on March 3, 2011, during which DAAAP provided advice and recommendations for the sponsor's phase 3 trials (clinical staff from DDDP attended the EOP2 meeting). According to those minutes DAAAP agreed with the sponsor's choice of endpoints as well as basic study design for their proposed phase 3 studies. The combination drug status was discussed and it was decided that it was not necessary to include an arm with oxymetazoline alone; however, there should be clinical evidence that tetracaine and oxymetazoline performed better than tetracaine alone. The sponsor ultimately completed the phase 3 trials, and on May 29, 2015, submitted an NDA.

The phase 3 trials include two studies conducted in adults and one trial conducted in 90 children ages 3 – 17. All subjects included in the trials were in need of an operative restorative dental procedure requiring local anesthesia. The first pivotal study in adults consisted of 110 subjects assigned to receive either Kovanaze, tetracaine alone (i.e., no oxymetazoline), or a placebo spray. The second adult trial enrolled 150 subjects who received either Kovanaze or a placebo spray. All trials were double-blind, randomized, placebo-controlled, parallel-group, and multicenter.

Two or three intranasal sprays of 200 uL of study drug were administered ipsilateral to the treatment tooth at intervals of four minutes. The decision to use a third spray was made if the subject was not sufficiently anesthetized after two sprays - the study dental procedure was initiated either seven minutes after the second spray or ten minutes after the third spray. If three sprays of the study drug did not provide sufficient anesthesia to allow completion of the study dental procedure, an injectable dental local anesthetic was used as rescue medication. The rescue medication was 4% articaine with 1:200,000 epinephrine (Septocaine®, NDA 20-971).

The primary efficacy variable was the percentage of subjects who completed the study dental procedure without the need for the rescue injection. The secondary efficacy variable in one of the adult studies was the completion of the study dental procedure without need for rescue by injection of local anesthetic stratified by age (≤50 and >50 years). In the other adult study, the secondary endpoint was absence of a pain response to pressure exerted by a mechanical probe. In the pediatric study, the two secondary

endpoints were 1) completion of the study dental procedure without need for rescue by injection of local anesthetic stratified by dose (0.1 mL, 0.2 mL, or 0.4 mL) and 2) completion of the study dental procedure without need for rescue by injection of local anesthetic stratified by age (3 to 5 years, 6 to 11 years, and 12 to 17 years, inclusive).

Safety monitoring was focused upon changes in heart rate, systolic blood pressure and diastolic blood pressure from baseline. In addition, a Naris Examination, and Alcohol Sniff Test were conducted to evaluate local irritation or loss of smell resulting from the intranasal administration. A Subject-Reported Safety Evaluation was also collected. Incidence rates for all adverse events and serious adverse events along with investigator-assessed severity and relationship to the study drug for individual events were reported for all treatments and tabulated by treatment group, age group and nasal spray anti-allergy medication. The events were tabulated and analyzed by treatment group, age group and use of nasal spray anti-allergy medication.

Requested Information in the Current Consult:

DDDP has received a consult request from DAAAP to provide input for original NDA 208032 Kovanaze nasal spray, as follows:

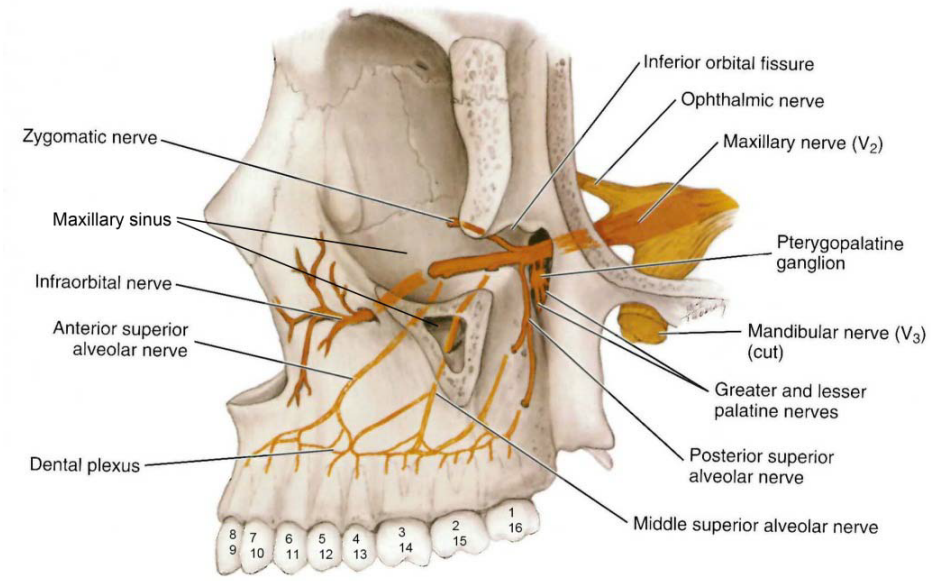
"The proposed indication is: for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J. Provided below are the specific questions for DDDP to address."

In the remainder of this review, each of the four questions will be restated, followed by the response from this reviewer.

1. What is the standard of care for injection anesthesia for dental procedures? Are the following local anesthetics considered standard of care for dental regional anesthesia in adult and pediatric patients: lidocaine, procaine, Septocaine, and Articaine?

Reviewer's Response:
The standard of care for pain management during dental procedures is the delivery of sufficient local anesthetic agent prior to a dental procedure in order for the patient to not feel pain. The use of reversible local anesthetic chemical agents is the most common method to achieve pain control in dental practice. Techniques of delivering the anesthetic vary according to length of the procedure and location of the teeth and/or soft tissue of the mouth to receive treatment.

Anatomical Considerations for Producing Anesthesia in the Correct Regions:
The sensation of pain is transmitted to the teeth via terminal branches of the Trigeminal (V) Cranial Nerve. The teeth and soft tissue in the maxillary arch are innervated by branches of the maxillary nerve (V_2, one of the major branches of V); the teeth and soft tissue of the mandibular arch are innervated by branches of the mandibular nerve (V_3, another major branch of V). (See the illustration that follows this paragraph)



The two techniques of delivering local anesthesia in dentistry are infiltration and regional block. A regional block will deliver anesthesia to the trunk of the nerve that controls sensation in an entire region on each side of the mouth. Infiltration is delivery of the local anesthetic agent via injection directly to the root apex of the tooth to be anesthetized. In this way, anesthesia is only produced in that tooth and the buccal soft tissue immediately surrounding the tooth. Infiltration is the preferred method of anesthetizing individual maxillary teeth, since it will not unnecessarily anesthetize the remainder of the maxillary region. A regional block would generally be employed only if several teeth require restoration during the same visit, or if a large area of soft tissue requires surgical treatment.

An example of a regional block is depositing local anesthesia directly to the anterior superior alveolar (ASA) nerve, a branch of the maxillary nerve, which will produce anesthesia to the central incisor, lateral incisor, and canine (#6 –8 or #9- 11, depending upon whether the right or left side is anesthetized) and surrounding soft tissue, including skin of the lower eyelid, upper lip and lateral side of the nose. The anterior superior alveolar (ASA) nerve originates approximately 5-8 mm posterior to the infraorbital foramen. To achieve the ASA block, the local anesthetic is deposited at the height of the buccal fold adjacent to the maxillary first premolar (5 – 8 mm posterior to the infraorbital foramen).

Meanwhile, the middle superior alveolar (MSA) nerve originates approximately 10 mm posterior to the infraorbital foramen. It is responsible for providing anesthesia to the maxillary premolars and supporting buccal tissue and bone. The local anesthetic is deposited via injection through the buccal mucosa at the height of the buccal fold adjacent to the maxillary second premolar.

The combined anterior and middle superior nerve block (AMSA) derives its name from the anesthesia of the anterior and middle superior alveolar nerves due to diffusion of the anesthetic solution via numerous nutrient channels on the palatal process of the maxillary bone. Both nerves are collateral branches of the infraorbital nerve in the homonymous canal and part of the maxillary nerve. The injection site is the confluence area of the ASA and MSA nerves, so the needle is inserted into tissue halfway between premolars

and midline of palate. AMSA provides anesthesia to the cuspids (#6 and 11) and premolars (#4-5 and 12-13), as well as all surrounding soft tissue (both the buccal and the palatal sides). According to the sponsor, Kovanaze's delivery through the sinus anesthetizes both the ASA and MSA and therefore, these same areas of the mouth as the AMSA injection.

Other regional blocks also exist, both in the maxillary and mandibular arches. In addition to the ASA, MSA, and AMSA blocks, regional blocks in the maxillary arch include the posterior superior alveolar (PSA) and maxillary nerve blocks. The PSA provides anesthesia to the three maxillary molars and supporting buccal tissue and bone. The local anesthetic is deposited via injection through the buccal mucosa at the height of the buccal fold adjacent to the maxillary second molar. If anesthesia is desired to the entire maxilla with one injection, a maxillary nerve injection is used; it provides anesthesia to all the maxillary teeth on that side, the buccal soft tissue, soft tissue and bone of the palate, skin of eyelid, side of nose, cheek and upper lip. The needle is inserted into the soft tissues and through the greater palatine foramen.

If anesthesia to the soft tissue covering the palatal side of the tooth is desired through a regional block, additional blocks are necessary. The greater palatine nerve block anesthetizes the posterior portion of the hard palate and its overlying soft tissues; the local anesthesia is delivered through injection in the soft tissue of the palate just anterior to the greater palatine foramen. The nasopalatine block provides anesthesia to the anterior portion of the hard palate and its overlying soft tissues; the local anesthesia is delivered through injection in the soft tissue of the palate just behind the anterior teeth. Note that injections to anesthetize the soft tissue of the palate do not produce anesthesia in any of the teeth.

In the mandibular arch, the inferior alveolar nerve (IAN), a branch of the mandibular nerve (V_3), supplies sensation to all of the mandibular teeth. Infiltration is not an option in the mandibular arch, since the mandibular bone is too dense to allow the anesthesia to reach the tooth apex; an IAN injection is currently the only method to sufficiently anesthetize a mandibular tooth for dental treatment. It is delivered via injection to the IAN by guiding the needle just adjacent to where the nerve exits the mandibular foramen. Since the subject of this drug is maxillary anesthesia only, further detail will not be discussed regarding mandibular anesthesia.

Choices of Local Anesthetic Agents in Dentistry

The two most commonly used dental local anesthetic agents in the US today are lidocaine and articaine, both with 2% epinephrine as a vasoconstrictor.[1] Vasoconstrictors are necessary in local anesthetics because these anesthetics have vasodilator properties which result in the drug diffusing away from the site of action in a very short time, resulting in insufficient duration to compete a dental procedure. In individuals for whom epinephrine is contraindicated, mepivacaine is an approved local anesthetic that has the ability to produce anesthesia for a limited time without the addition of a vasoconstrictor such as epinephrine; this is because it has less vasodilative qualities than the other anesthetics. Although it has a shorter duration of action, it is still used in individuals for whom epinephrine is contraindicated.

[1] Singh, 2002

Procaine, an ester-type local anesthetic agent first synthesized in 1905, was the most commonly used local anesthetic for more than four decades. However, esters are prone to producing allergic reactions, so procaine was largely replaced by lidocaine, an amide derivate that was introduced in 1948. Mepivacaine, another amide anesthetic discussed earlier, has been marketed since 1957.

Until the introduction of articaine, lidocaine was the most commonly used local anesthetic in dentistry worldwide. Articaine was first approved in Europe in 1976, Canada in 1983, and the US in 2000. Septocaine was the brand name of the first articaine hydrochloride anesthetic approved for dental in the US. Since then, other formulations containing articaine as the active ingredient, have been approved in the United States and include Zorcaine, Articadent and Orabloc. There are minor differences between these three, which all contain the same concentration of articaine as the active anesthetic.

Since the introduction of articaine, the usage of local anesthetics has been increasingly shifting from lidocaine to articaine as the most widely used in the US. For example, the usage based upon total US sales between 1997 and 2008 was: lidocaine 58%, mepivacaine 18%, and articaine 14% (with miscellaneous others totally 10%) (ADA) However, US sales data from 2009 showed that articaine comprised 41% of all local anesthetics used in dentistry. In other parts of the world, articaine has been the most widely used anesthetic for several years; the 2012 sales figures in Germany showed articaine's share of local dental anesthetics as 97%[2]. This reviewer was unable to locate articaine sales figures in the United States today; however, it is accurate to state that articaine and lidocaine comprise the vast majority of local anesthetic use, with mepivacaine still used in individuals for whom epinephrine is contraindicated.

Literature about usage in the pediatric population is scant, but it appears as though the same usage pattern in adults is being replicated; that is, lidocaine and articaine are the most popular local anesthetics, with a growing market share by articaine. In 2001, 83% used lidocaine on children, and 11% used mepivacaine[3]. The more current literature describing articaine's use in children reflects confidence in the safety and efficacy of articaine in children as young as 4, the labeled age. See the next response for further discussion about pediatric usage of Kovanaze.

2. Is there a physiologic or anatomic explanation for Kovanaze's similar success rate compared to placebo in the age group 3 to 5-years-old? Below is a table of success rates by age group in trial SR 3-04.

Table 11.11 Success Rates by Age Group (mITT)

Successful Anesthetic Response by Age Strata N (%)	**K305 (N = 60)**	**PBO (N = 30)**	**One-Sided Fischer's Exact Test P-Value**	**Stratified CMH P-Value****
3 to 5 years (n = 31)	(b) (4)			0.046
6 to 11 years (n = 38)				
12 to 17 years (n = 21)	15/16 (93.8%)	2/5 (40.0%)	0.028	

[2] Malamed 2014
[3] Kohli, 2001

Reviewer's Response:

In Section 13.1 of Study Report SR3-04 (Efficacy Discussion), the sponsor addresses the results of the subjects between 3 to 5 years, which shows (b) (4) . These reasons include difference in anatomy between primary dentition and permanent dentition, difficulty in communication with young children, and anatomical differences in the sinus development. This reviewer concurs with the sponsor's explanations. In addition, the sponsor does not mention as a possibility that with such small numbers in each of the age cohorts, chance cannot be ruled out as a factor of the results. For example, with a total of only 10 subjects in the placebo group of the 3 to 5 year olds, a different response rate in just 3 or 4 subjects would alter the conclusion.

Literature supports the finding that children undergoing dental procedures on primary teeth without anesthesia may experience little or no pain - this provides one reason that the placebo response was so high in the younger age subjects. The explanation is based upon children between the ages of 3 – 5 having only primary teeth, which differ significantly from adult (permanent) dentition. The difference of note for pain response is that during the time that permanent replacement teeth are forming immediately underneath the primary teeth, the roots of the primary teeth begin to resorb. As the permanent tooth completes its development and eruption into the same place as its primary predecessor, the primary teeth continue to dissolve.

Sensation from a tooth originates in the pulp of the tooth, which is located in its interior, where it communicates with the dental nerve plexus at the apex of the tooth's root. When resorption of the primary roots begins, there is no longer this communication with the dental plexus; therefore, depending upon the extent of the primary tooth resorption, there may be no sensation experienced during a dental procedure on that tooth.

By the age of 12, most individuals have their complete adult set of dentition (with the exception of third molars). It is therefore, consistent that the 12 – 17 year old children responded nearly identically to the adults.

The period of 6 – 11 years of age, between these two pediatric age groups, is referred to as the mixed dentition phase, with tooth exfoliation occurring regularly. Children in this age group may have several teeth at any given time which do not possess sensory innervation, depending on the developmental stage of the tooth in question.

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Regarding sinus development, literature suggests that children may not have a fully developed nasal cavity and paranasal sinuses until the age of 12. Furthermore, the nasal cavity and paranasal sinuses, when compared to those in adults, differ not only in size, but also proportion. This also supports the findings (b) (4) in pediatric patients under the age of 12.

Note that the interpretation of effectiveness may also be different in children than adults. Because anesthetic injection is the dental procedure that produces the greatest negative response in young children[4], the avoidance of the injection may be beneficial, as it would

greatly reduce the use of a needle. Even with the possibility that a primary tooth does not require anesthesia, it is standard of care to provide it prior to dental procedures, not knowing advance which primary teeth still possess pain perception.

3. Is the explanation for the discussion of the analysis by tooth location and number on pages 70-71 of the CSR for 3-03 plausible? Follow the link to the clinical study report for SR 3-03: \\CDSESUB1\evsprod\NDA208032\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\intranasal-dental-anesthetic\5351-stud-rep-contr\sr3-03\sr303-study-body.pdf.

Reviewer's Response:

Refer to the sponsor's Table 11.10 reproduced below (from Study 3-03, page 70):

Subgroup Analysis of Success Rates by Tooth Location and Tooth Number, (mITT)

Stratification Stratum	Anesthetic Success Rate				*P*-value[a]
	K305 (N = 100)		PBO (N = 50)		
	N	Count (%)	N	Count (%)	
TOOTH LOCATION					
Anterior (6 to 11)	53	51 (96.2%)	26	8 (30.8%)	< 0.0001
Premolar (4,5,12, and 13)	47	37 (78.7%)	24	6 (25.0%)	
TOOTH NUMBER					
4 second premolar	15	10 (66.7%)	5	0 (0.0%)	NA
5 first premolar	12	11 (91.7%)	8	2 (25.0%)	
6 canine	5	5 (100.0%)	1	0 (0.0%)	
7 lateral incisor	13	13 (100.0%)	7	3 (42.9%)	
8 central incisor	16	16 (100.0%)	5	2 (40.0%)	
9 central incisor	8	7 (87.5%)	3	1 (33.3%)	
10 lateral incisor	5	4 (80.0%)	7	1 (14.3%)	
11 canine	6	6 (100.0%)	3	1 (33.3%)	
12 first premolar	10	10 (100.0%)	6	2 (33.3%)	
13 second premolar	10	6 (60.0%)	5	2 (40.0%)	

When the efficacy results are examined by tooth location, a difference in success rates for some of the teeth is evident, particularly the second premolars. The overall results showed that 96% of subjects who had a dental procedure on their anterior teeth did not require rescue anesthesia, compared to 31% of those who received placebo. However, only 79% of subjects who received the spray for dental procedure on their premolar teeth did not require rescue anesthesia, compared to 25% of those who received placebo. (Both sets of results are still highly statistically significant at $p < 0.0001$ when the test and placebo responses are compared) The sponsor posits that this difference results from both a small number of subjects in each subgroup as well as variability in innervation of the teeth. This reviewer agrees with both of these explanations.

Compared to the response in the anterior teeth, the second premolar on both the right and left side both performed worse, with a 60% rate in the second left premolar (compared to

[4] Kohli, 2001

40% placebo response) and a 67% success in the second right premolar (compared to 0% for the placebo). This is consistent with the anatomic configuration of the branches of the superior alveolar nerve, which supplies the maxillary teeth. It may be useful to refer back to the illustration of the innervation of the maxillary region that appears earlier in this review for the more detailed discussion in the following paragraphs.

The literature has shown that in approximately one-third to one-half of individuals, the MSA nerve is not present; and in the majority of those cases the PSA nerve innervates the premolars along with the molars. Since the nasal spray is not expected to anesthetize the PSA nerve, the premolars in these individuals would require rescue local infiltration.

With the exception of the right and left second premolar cells, all subjects receiving the test drug reported either 100% success or just one subject in each cell not reporting success (a success rate of 80 - 92%). The corresponding groups with those teeth receiving a placebo spray ranged in results from 0% success to 43% success, which is consistent with the overall conclusion that the test group is statistically superior to the placebo group.

Since the study was not powered to statistically detect individual tooth comparisons, caution must be used in interpreting these results. When subdivided by tooth location, small numbers of subjects appear in each cell; Table 11.10 shows that there are a few as 5 subjects in two of the test groups.

Of note, however, is Table 3, (b) (4) In that table (below), the sponsor combined both pivotal adult studies, which increased the numbers in each cell when stratified by tooth. In this table, the total of 41 subjects who received dental treatment on the right and left second premolars showed a success rate of only 63%, much less than the other 4 categories of teeth (central incisors, lateral incisors and first premolars). (b) (4)

Table 3: Kovanaze Success Rate by Tooth Number in Adult Dental Patients (Pivotal Studies 1 and 2)

Tooth No.	Kovanaze Success	Placebo Success
8 & 9	28/29 (97%)	4/14 (29%)
7 & 10	25/26 (96%)	4/16 (25%)
6 & 11	15/15 (100%)	1/6 (17%)
5 & 12	31/33 (94%)	8/22 (36%)
4 & 13	26/41 (63%)	3/14 (21%)

4. The Applicant describes a Subjective Numbness Assessment (SNA) on page 112 of SR 3-02 protocol version 3.0:

To assess conditions that could be associated with investigative drug, ask the subject the following questions.

- "Do you notice any abnormal sensation when you tap your front teeth together?"
- "Do you notice any abnormal sensation in the roof of your mouth?"

Record the Yes/No response in the source documents.

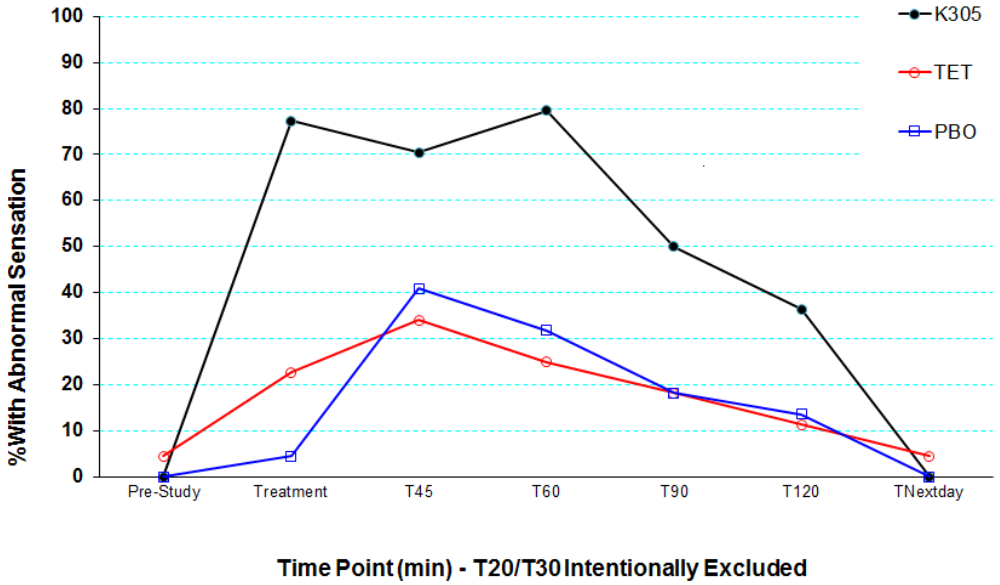
Are the questions in the SNA a clinically useful measure of regional anesthesia of anterior maxillary teeth?

Reviewer's Response:
The CDER Division which possesses the expertise to respond to the validity of a patient reported outcome is the Clinical Outcome Assessment (COA) Team. However, to provide some input towards the response, this reviewer examined past measurements of local anesthetic response in similar drugs reviewed in CDER as well as considered the possible shortcomings in the methodology that the sponsor used.

Study SR 3-02 contained an arm in which subjects received tetracaine alone, in addition to the arm with Kovanaze and a placebo spray arm. Subjective numbness assessment (SNA) was performed Pre-study, during treatment, T20, T30, T45, T60, T90, T120 and the next day. In summary, the SNA provides only a minimal amount of additional useful clinical information to supplement the results of the primary outcome variable, need for rescue anesthetic. However, lack of control and repeatability inherent in the SNA prevents the results from being considered conclusive. Therefore, the SNA ultimately measures the same outcome, hard and soft tissue anesthesia, but in a less predictable way than the primary outcome.

The results of the SNA appear below. The first item, Figure 11.3 from the sponsor's submission, displays a comparative graphing of the percentage of subjects at each time point that report "yes" to the question about abnormal sensation of the soft tissues. Although the shortcomings of this assessment have been described, the results add support to Kovanaze providing the greatest soft tissue anesthesia of the three study arms.

Figure 11.3 Subjective Numbness Assessment - Abnormal Sensation When Tapping Front Teeth Together (mITT Population) from the sponsor's SR 02 Study Report



This table below, also taken form the sponsor's submission, shows the percentage of subjects who report feeling an abnormal sensation when tapping the front teeth together. Although the sponsor did not perform a statistical analysis, the trend of the results supports consistently greater abnormal sensations in the Kovanaze group compared to either the tetracaine or placebo groups.

SNA Parameter		**K305 (N=44) n (%)**	**TET (N=44) n (%)**	**PBO (N=22) n (%)**
Time Point				
	Abnormal Sensation When Tap Front Teeth			
Pre-Study	Yes	0	2 (4.5%)	0
	No	44 (100%)	42 (95.5%)	22 (100%)
Treatment	Yes	34 (77.3%)	10 (22.7%)	1 (4.5%)
	No	10 (22.7%)	34 (77.3%)	21 (95.5%)
T20	Yes	14 (31.8%)	5 (11.4%)	0
	No	2 (4.5%)	23 (52.3%)	16 (72.7%)
	Missing	28 (63.6%)	16 (36.4%)	6 (27.3%)
T30	Yes	22 (50.0%)	1 (2.3%)	1 (4.5%)
	No	3 (6.8%)	4 (9.1%)	3 (13.6%)
	Missing	19 (43.2%)	39 (88.6%)	18 (81.8%)
T45	Yes	31 (70.5%)	15 (34.1%)	9 (40.9%)
	No	9 (20.5%)	21 (47.7%)	11 (50.0%)
	Missing	4 (9.1%)	8 (18.2%)	2 (9.1%)
T60	Yes	35 (79.5%)	11 (25.0%)	
	No	9 (20.5%)	32 (72.7%)	15 (68.2%)
	Missing	0	1 (2.3%)	0
T90	Yes	22 (50.0%)	8 (18.2%)	4 (18.2%)
	No	22 (50.0%)	36 (81.8%)	18 (81.8%)
T120	Yes	16 (36.4%)	5 (11.4%)	3 (13.6%)
	No	28 (63.6%)	39 (88.6%)	19 (86.4%)
TNextday	Yes	0	2 (4.5%)	0
	No	43 (97.7%)	41 (93.2%)	22 (100.0%)
	Missing	1 (2.3%)	1 (2.3%)	0

To answer the question about clinical usefulness, it is first important to look at the validity of the instrument. To do so, it is useful to examine a recent similar endpoint that was recently reviewed by DAAAP. OraVerse (NDA 22-159) was approved in DAAAP in 2008 "for reversal of the soft-tissue anesthesia, i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor." The primary endpoint in the clinical trials was the return of normal sensation to the lip. Assessment of the return to normal sensation was by patient palpation of the soft tissues, i.e., tongue, lip, cheek, and nose, and by grinding to assess sensation of the teeth. The manner in which palpation was to be performed was explicitly defined in the study protocols. Subjects were trained in the technique and were included in the efficacy assessment only if they were able to successfully perform the test.

Although the hard tissue assessments are nearly identical (grinding the teeth with OraVerse and tapping the teeth together with Kovanaze), the soft tissue assessment varies. OraVerse described training and subsequent assessment of the subjects' abilities to perform this evaluation, whereas Kovanaze did not. Also, the soft tissue palpation in multiple areas of the oral cavity was more inclusive for OraVerse, rather than just palpation in one spot in the palate for Kovanaze. Finally, for OraVerse, DAAAP also required that the sponsor conduct additional measures of residual numbness with methodology validated during the drug development period. These additional measures included ability to speak clearly, drink water without drooling and similar signs of lingering anesthesia.

Each of the two questions in the SNA attempts to elicit additional information about anesthesia success in the teeth (first question) and in the soft tissue (second question). One major problem with both questions is that the term "abnormal" without further explanation could mean either a sensation of anesthesia, paresthesia, or pain; therefore, actually opposite outcomes could both result in a yes response.

Even assuming that the vast majority of subjects understood the questions to mean respectively, "do the front teeth feel numb," and "does the roof of the mouth feel numb?," it is not clear that either touching the top and bottom teeth together or tapping the roof of the mouth[5] would be done with any kind of standardized force to elicit a reliable response. In addition, if either the teeth upon tapping or soft tissue upon palpation felt "numb" to the subject, it cannot be determined if this would have been sufficiently anesthetized to prevent pain from a dental procedure. There is a great amount of variability inherent in this assessment process.

Although the second question in the SNA may have helped to answer the sponsor's secondary objective about soft tissue anesthesia, a related assessment to the SNA that was administered at the same time was a soft-tissue anesthesia assessment (STAA, Appendix 2 from the sponsor's study report reproduced here). Note that in the protocol for Study SR 3-02, the secondary efficacy endpoint was defined as "post-study drug administration absence of a pain response to pressure exerted by a mechanical probe (i.e. Sensor Probe, Zila Pharmaceuticals, Inc.) on the incisive papilla and greater palatine foramen ipsilateral

[5] In the discussion section of SR 3-02, the sponsor clarifies that the subjects were instructed to tap the roof of the mouth to answer the second question about sensation in the roof of the mouth

to the dental procedure." Therefore, the STAA was actually the soft tissue measurement upon which the sponsor relied.

The STAA was assessed by the investigators with use of a calibrated, preset-force periodontal probe (PDT Sensor Probe, DenMat) on the incisive papilla and greater palatine foramen. Unlike having each subject tap on their palate with a potentially variable force and location, the same trained examiner using a periodontal probe which exerts a consistent measured force each time can provide controlled results. The STAA seems to be a better measurement for soft tissue anesthesia than the SNA.

Frederick N. Hyman, DDS, M.P.H.

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/s/

FREDERICK N HYMAN
03/14/2016

DAVID L KETTL
03/14/2016

Clinical Inspection Summary (CIS)

Date	March 8, 2016
From	John Lee, M.D., Medical Officer Jan Pohlman, M.D., Team Leader Division of Clinical Compliance Evaluation
To	Amelia Luckett, M.D., Medical Officer Rigoberto Roca, M.D., Deputy Division Director Division of Anesthesia, Analgesia, and Addiction Products
Application	NDA 208032
Applicant	St. Renatus, LLC
Drug	Tetracaine 3% and oxymetazoline 0.05% nasal spray (Kovanaze®)
New Molecular Entity	No
Review Priority	Standard
Proposed Indication	Regional dental anesthesia
Consultation Date	August 31, 2015
Action Goal Date	March 29, 2016
PDUFA Due Date	March 29, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The pivotal studies supporting this 505(b)(2) NDA (Studies SR 3-02, SR 3-03, and SR 3-04) were audited at good clinical practice (**GCP**) inspections of three clinical investigator (**CI**) sites with large subject enrollment (four study-sites, two studies at one site). No significant GCP deficiencies were observed.

At one CI site, a Form FDA 483 was issued for isolated minor deficiencies unlikely to be significant. Study conduct appeared adequate at all three sites, including IRB/sponsor oversight of study conduct. All audited NDA data were verifiable against source records and case report forms (**CRFs**). The data from the three study sites appear reliable as reported in the NDA.

II. BACKGROUND

St. Renatus, LLC submitted this original NDA 208032 for Kovanaze®, a fixed tetracaine-oxymetazoline combination nasal spray for use as a regional dental anesthetic. The proposed indication for use is [redacted] teeth 4-13 [redacted] or [redacted] teeth A-J [redacted].

Tetracaine and oxymetazoline have been commercially available in the United States, since 1936 for tetracaine and since 1964 for oxymetazoline. In support of this 505(b)(2) NDA, St. Renatus references Synera® (lidocaine/tetracaine patch) and the over-the-counter oxymetazoline nasal decongestants.

The three pivotal studies for this NDA (SR 3-02, SR 3-03, and SR 3-04) were conducted between 2012 and 2013 in a combined total of 350 subjects randomized at six clinical investigator (**CI**) sites. The following CI sites in the three studies were chosen for inspection based primarily on large enrollment. Additionally:

- Site 05: In addition to large enrollment in Study SR 3-03, this site also participated in Study SR 3-04 as the only site that participated in more than one pivotal study.
- Site 04: This site had a disproportionally large number of subjects reporting no pain for the Soft Tissue Anesthesia (**STA**) assessment.
- Site 02: At this site, the ratio of the number of subjects that did not complete the study was higher than at the other CI sites in Study SR 3-02.

III. INSPECTION OUTCOMES

	Clinical Investigator Site	Study, Site, Enrollment	Inspection Outcome
1	Adam D. Marberger, D.D.S. Family and Cosmetic Dentistry 4110 South Highland Drive Salt Lake City, Utah	SR 3-02, Site 02 60 subjects	February 18 - 26, 2016 VAI*
2	Sebastian G. Ciancio, D.D.S. SUNY School of Dentistry 3435 Main Street Buffalo, New York	SR 3-02, Site 04 50 subjects	December 7 - 10, 2015 NAI
3	Yiming Li, D.D.S., M.S.D., Ph.D. Loma Linda School of Dentistry 24876 Taylor Street, Room 122 Loma Linda, California	SR 3-03, Site 05 68 subjects SR 3-04, Site 05 42 subjects	January 13 - 19, 2016 NAI

NAI = No Action Indicated (no significant deviations from GCP regulations)
VAI = Voluntary Action Indicated (minor deviations from GCP regulations)
OAI = Official Action Indicated (significant deviations from GCP regulations and/or data unreliable)

*For this Site 02 in Study SR 3-02, the final Establishment Inspection Report (**EIR**) has not been received from the field office. The inspection outcome shown is based on preliminary communications with the field investigator, pending confirmation at EIR receipt and review.

1. Adam D. Marberger, D.D.S.

a. What was inspected:

General records: study conduct, oversight by sponsor and institutional review board (**IRB**), CI financial disclosure, drug accountability, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, adverse event (**AE**) monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study SR 3-02, Site 02: 80 subjects were screened, 60 were enrolled, and 59 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for 14 subjects.

A Form FDA 483 was issued for not following the protocol, specifically for not reporting mild and transient self-limited hypertension as AEs (three subjects):

- Once, blood pressure (**BP**) up to 144/90 mm Hg (increase < 25/15) for 30 minutes
- Twice, BP up to 148/86 mm Hg (increase < 25/15) for 90 minutes (combined)
- Once, BP up to 140/95 mm Hg (increase > 25/15) for 140 minutes

These episodes of uncomplicated hypertension appear unlikely to be significant. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable against source records and CRFs.

c. Assessment of data integrity: The data from this study site appear reliable.

2. Sebastian G. Ciancio, D.D.S.

a. What was inspected:

General records: study conduct, oversight by sponsor and IRB, CI financial disclosure, drug accountability, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study SR 3-02, Site 04: 57 subjects were screened, 50 were enrolled, and 50 completed the study. Case records were reviewed in detail for all subjects, including complete review for 10 subjects completing study.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable against source records and CRFs.

c. Assessment of data integrity: The data from this study site appear reliable.

3. Yiming Li, D.D.S., M.S.D., Ph.D.

a. What was inspected:

General records: study conduct, oversight by sponsor and IRB, CI financial disclosure, drug accountability, and subject records

Subject case records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification

Data verification: subject randomization, primary efficacy endpoint, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study SR 3-03, Site 05: 76 subjects were screened, 68 were enrolled, and 66 completed the study. Study SR 3-04, Site 05: 42 subjects were screened, 42 were enrolled, and 41 completed the study. Case records were reviewed for all enrolled subjects in both studies, including detailed review for 10 subjects completing study.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. All audited data were verifiable against source records and CRFs.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: For Site 02 in Study SR 3-02, the final EIR has not been received from the field office and the final inspection outcome remains pending. The inspection results in this Clinical Inspection Summary (**CIS**) are based on preliminary communications with the field investigator. Upon receipt and review of the EIR, an addendum will be forwarded to the review division if the final outcome changes; otherwise, close-out correspondence with the CI (copied to review division) indicates EIR review completion without new significant findings and outcome finalization as reported in this CIS.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

JONG HOON LEE
03/08/2016

JANICE K POHLMAN
03/09/2016

KASSA AYALEW
03/09/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

MEMORANDUM

Office of Pediatric Therapeutics
Office of the Commissioner
10903 New Hampshire Ave., WO/32-5121
Silver Spring, MD 20993-0002
Tel (301) 796-8665; FAX (301) 847-8619

Date: March 4, 2016

From: Robert M. Nelson, M.D., Ph.D.
Senior Pediatric Ethicist/Deputy Director

Michelle D. Roth-Cline, M.D., Ph.D.
Pediatric Ethicist/Health Scientist
Office of Pediatric Therapeutics, OC/OSMP/OPT

To: Amelia Luckett, M.D., Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products, CDER

Re: **NDA 208,032:** Tetracaine and oxymetazoline nasal spray for dental procedures

Materials Reviewed

NDA 208032: Kovanaze Nasal Spray (Code Name: K305). Response to FDA Information Request (Received February 12, 2016). Sponsor: St. Renatus. Received February 26, 2016.

Background

As part of the pediatric ethics consultation response, an information request was sent to the Sponsor on February 12, 2016 asking for further information and documentation concerning the Institutional Review Board (IRB) review of protocol SR 2-07. The response to this information request (IR) was received by OPT on February 26, 2016.

Recommendation

Based on the analysis of the response to the FDA IR, we recommend that the following text be sent to the sponsor with the instruction to share the letter with the responsible IRB, (b) (4). We are available to help draft the letter to the Sponsor.

"Upon review of the response to the FDA Information Request, FDA has the following observations:

1. The initial IRB review of the protocol on August 20, 2013 appropriately (and correctly) identified the fact that there was no prospect of direct benefit to the enrolled children, and that the administration of the investigational product presented more than minimal risk. There was no mention of the level of risk exposure from the other interventions and procedures included in the protocol.
2. Study SR 2-07 was initiated on September 24, 2013 and completed November 1, 2013. At the continuing IRB review of the protocol on February 13, 2014, the IRB noted that the pediatric "risk" category was not assigned at the time of the initial review. The IRB determined that the protocol "was a Pediatric Risk Determination Category 3 due to the nature of the study" (21 CFR 50.53). The only noted deficiency was the failure to obtain the signature of both parents. As noted by the Sponsor, this deficiency was corrected in retrospect by obtaining the second signature on a revised document. The additional document (dated March 18, 2014) stated: "we are asking you to give your permission for your child to have participated in the study." In signing the document, the parent would

be consenting "to having had my child participate in the research study under the terms of the original Informed Consent." Alternatively, the parent or guardian could sign a declaration (dated April 22, 2014) that he or she is the sole legal parent or guardian for the child who participated in the study.

3. A Memorandum to Study File, dated March 18, 2014 expanded on the IRB risk determination, noting the criteria for approval under 21 CFR 50.53. Specifically, the memorandum states: "It is reasonable that a study subject may have the interventions in this study in medical or dental experiences. The research is likely to yield generalizable knowledge about the study drug that could potentially avoid the use of a local anesthetic injection for maxillary dental procedures in the pediatric population."

FDA has the following comments on the IRB review of this protocol.

1. Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual children may be evaluated under 21 CFR 50.53. Criteria for approval under this category include the following:

   - The risk represents a minor increase over minimal risk;
   - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   - The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition;
   - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

   In addition to the assessment of the level of risk exposure, approval under this category requires children to have a "disorder or condition". This term is not defined under FDA regulations, but the Institute of Medicine in 2004 defined "disorder or condition" as a set of "specific physical, psychological, neurodevelopmental, or social characteristics" that scientific evidence or clinical knowledge has shown to compromise the child's health or "to increase risk of developing a health problem in the future." Therefore, under the minor increase over minimal risk category, children may either have a disorder (i.e., illness) that is the object of the research, or be currently healthy but "at risk" for such an illness based on scientific and/or clinical evidence. This definition excludes the use of healthy not-at-risk children from greater than minimal risk research without a prospect of direct benefit.

   Inclusion/exclusion criteria in study SR 2-07 appear to allow the participation of children irrespective of whether they meet this disorder or condition requirement. The protocol for study SR 2-07 does not specify screening criteria for having a disorder or condition that is the object of the research. Specifically, there is no discussion of screening children either for currently needing dental procedures, or for factors that may predispose children to requiring dental procedures in the future (i.e. to be "at risk" of needing dental procedures.) Absent evidence-based enrollment criteria establishing that the children to be enrolled in this protocol are "at risk" from needing local anesthesia for future dental procedures, the IRB assessment that "a study subject may have the interventions in this

study in medical or dental experiences" lacks sufficient justification. Therefore, this pharmacokinetic study does not fulfill the requirements for approval as a minor increase over minimal risk (21 CFR 50.53), because the protocol did not require that enrolled children have a disorder or condition that is the object of the research.

2. FDA appreciates the desire to be in compliance with the requirement under 21 CFR 50.53 that "both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child" (21 CFR 50.55). However, the concept that a parent or guardian could give permission retrospectively for something that has happened in the past is conceptually incoherent and inconsistent with FDA regulations. A more appropriate approach may have been to inform the parent or guardian of the oversight, share with him or her details of the clinical investigation, and document this conversation.

FDA appreciates study SR 2-07 was reviewed and approved several years ago, and that the (b) (4) IRB currently may be more attuned to the need for a timely assessment of the pediatric risk category and the disorder or condition requirement under 21 CFR 50.53. FDA would encourage on-going educational efforts to ensure that children in future FDA-regulated studies reviewed and approved by the (b) (4) IRB under 21 CFR 50.53 meet this disorder or condition requirement."

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/s/

ROBERT M NELSON
03/04/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

MEMORANDUM

Office of Pediatric Therapeutics
Office of the Commissioner
10903 New Hampshire Ave, WO 32-5126
Silver Spring, MD 20993
Tel (301) 796-8665; FAX (301) 847-8619

Date: March 3, 2016

From: Michelle Roth-Cline, M.D., Ph.D., Pediatric Ethicist/Health Scientist
Office of Pediatric Therapeutics, OC

Through: Robert Nelson, M.D., Ph.D., Deputy Director
Office of Pediatric Therapeutics, OC

To: Amelia Luckett, M.D., Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products, CDER

Re: **NDA 208,032:** Tetracaine and oxymetazoline nasal spray for dental procedures

Materials Reviewed

1) Request for Ethics Consultation from Amelia Luckett, M.D., dated February 3, 2016
2) St. Renatus Protocol, The Pharmacokinetics of Tetracaine, para-Butylaminobenzoic acid, and Oxymetazoline after Intranasal Administration of Kovacaine Mist (Tetracaine Hydrochloride with Oxymetazoline Hydrochloride) to Healthy Pediatric Subjects, SR 2-07, dated August 26, 2013
3) Informed Consent Document for The Pharmacokinetics of Tetracaine, para-Butylaminobenzoic acid, and Oxymetazoline after Intranasal Administration of Kovacaine Mist (Tetracaine Hydrochloride with Oxymetazoline Hydrochloride) to Healthy Pediatric Subjects, SR 2-07, approved by (b) (4) IRB September 25, 2013
4) Response to FDA Information Request of February 12, 2016, from St. Renatus, dated February 26, 2016
5) Institute of Medicine (2004) IOM Committee on Clinical Research Involving Children: Ethical Conduct of Clinical Research Involving Children. 2010/07/30 edn. National Academies Press (US), Washington DC

Background *(adapted from the protocol)*

The study protocol in question is a single-center open-label single-dose pharmacokinetic (PK) and safety study of Kovacaine Mist in 18 healthy pediatric subjects aged 3 to 17 years. Kovacaine Mist is an anesthetic solution containing 3% tetracaine hydrochloride and 0.05% oxymetazoline hydrochloride in a single spray dose. A single spray dose of 100 µL Kovacaine Mist contains 3 mg tetracaine HCl and 0.05 mg oxymetazoline HCl. Doses utilized in the study ranged from 100 to 400 µL depending on the weight of the subject.

Subject Weight	Treatment Group: Kovacaine Mist	Volume per Spray	Number of Sprays	Kovacaine Mist Total Dose	
				Tetracaine HCl	Oxymetazoline HCl (Oxymetazoline Equivalent)
10 kg to <20 kg	100 µL	100 µL	1	3 mg	0.05 mg (0.044 mg)
20 kg to <40 kg	200 µL	100 µL	2	6 mg	0.1 mg (0.088 mg)
40 kg or more	400 µL	200 µL	2	12 mg	0.2 mg (0.175 mg)

Per the protocol, inclusion criteria included the following:

1) Male or female 3-17 years of age inclusive.
2) Sufficiently healthy as determined by the investigator to receive the test medications.
3) Accompanied and/or represented by a parent or guardian able to comprehend and sign the informed consent document.
4) Subject able to understand and provide assent to an age-appropriate subject assent form (as defined by local practice or regulation).
5) Patient or parent/guardian able to communicate with the investigator and comply with the requirements of the protocol.
6) Within the 10th and 90th percentiles for weight by age.
7) Can breathe through both nostrils.
8) Body mass index between 14 and 30 kg/m2 inclusive.

Among other things, children with "clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory evaluation during screening" or "anticipated need for use of oxymetazoline or phenylephrine nasal spray, nasal irrigation, or other nasal or oral decongestant on the day of the study procedure" are excluded.

Blood samples (1 mL) will be collected at the following times relative to dosing: pre-dose and T0, T10 min T0.5, T1, T3, T6, T8, T9, T12, and T24 hours after dosing. Safety monitoring measurements will include sitting vital signs (HR, SBP, DBP, temperature and SpO2) before sample collection at each time point; hematology, clinical chemistry and urinalysis at screening, at baseline, and at the end-of-study visit (2 weeks after dosing). Safety monitoring measurements will include sitting vital signs (HR, SBP, DBP, temperature and SpO2) at follow-up visits (24 hours and 1 week after dosing), and at the end-of-study visit (2 weeks after dosing). Enrolled children will be checked into a clinical site the morning of the study prior to dosing, and released after the sample collection at T12 hours. Children will return to clinic the following day for the T24 hour sample collection and for a follow-up visit one week after dosing.

Reviewer's Comment: The children enrolled in this study do not receive a direct benefit from study participation, as these children are not having a dental procedure and thus do not require anesthesia. The inclusion criteria are quite unselective, allowing the enrollment of almost any child who is sufficiently healthy and within the specified age range. These criteria do not require any history of dental procedures or other conditions that may predispose children to needing dental procedures in the future.

Brief Regulatory History

This protocol for SR 2-07 was received by FDA on September 4, 2013. The Agency has 30 days to review newly submitted INDs to determine whether the study may proceed or whether a clinical hold should be imposed. However, this study was submitted to an IND (070868) which was previously opened. As such, the Agency may not review the submission within 30 days, and the Sponsor may legally initiate the study as soon as it has been submitted. Study SR 2-07 was initiated on September 24, 2013 and completed November 1, 2013 (within five weeks). There is no evidence that the Agency reviewed the submission prior to study initiation and completion. The Pediatric Ethics team was first made aware of this study when the deferral application for the NDA was reviewed at the Pediatric Review Committee on January 13, 2016.

Reviewer's Comment: Protocol Analysis Under 21 CFR 50 subpart D

FDA-regulated clinical trials involving children are subject to the Additional Safeguards for Children in Clinical Investigations, found in FDA regulations at 21 CFR 50 subpart D. Under this framework, interventions and procedures may be approved under 21 CFR 50.52 if they offer the prospect for direct clinical benefit to enrolled children. Studies that do not offer the prospect for direct benefit to enrolled children may be evaluated under 21 CFR 50.51 (minimal risk) or 21 CFR 50.53 (minor increase over minimal risk) if additional criteria are met. Studies that cannot be approved under any of the above categories must be referred by an institutional review board (IRB) for Federal panel review under 21 CFR 50.54.

As noted above, study SR 2-07 does not offer enrolled children the prospect of direct benefit, because the study drug is not being given to children who have a medical need for the product. As such, study SR 2-07 cannot be approved under 21 CFR 50.52, because studies under this category must offer a prospect of direct benefit.

The next question is whether study SR 2-07 can be approved either as minimal risk under 21 CFR 50.51, or as a minor increase over minimal risk under 21 CFR 50.53. Minimal risk is defined under 21 CFR 50.3 (k) as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." The administration of FDA-regulated investigational products to children without a medical need for these products is neither "ordinary" nor "routine", and is generally not considered minimal risk. Therefore, study SR 2-07 cannot be considered to meet the requirements for minimal risk under 21 CFR 50.51.

Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual children may be evaluated under 21 CFR 50.53. Criteria for approval under this category include the following:

- *The risk represents a minor increase over minimal risk;*
- *The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;*

- *The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition;*
- *Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.*

In addition to the assessment of the level of risk exposure, approval under this category requires children to have a "disorder or condition". This term is not defined under FDA regulations, but the Institute of Medicine defined "disorder or condition" as a set of "specific physical, psychological, neurodevelopmental, or social characteristics" that scientific evidence or clinical knowledge has shown to compromise the child's health or "to increase risk of developing a health problem in the future" (2004). Therefore, under the minor increase over minimal risk category, children may either have a disorder (i.e., illness) that is the object of the research, or be currently healthy but "at risk" for such an illness based on scientific and/or clinical evidence. This definition excludes the use of healthy not-at-risk children from greater than minimal risk research without a prospect of direct benefit. An ethical basis for the "disorder or condition" requirement is that children with such a condition may benefit in the future from a drug that is approved to treat their condition. "Healthy" children who do not have such a condition and are not "at risk" for the condition would not have the same probability of benefitting in the future from their participation in research.

The protocol for study SR 2-07 does not specify criteria that would include only children who meet this disorder or condition requirement, such as children who have undergone previous dental procedures requiring local anesthetic. Specifically, there is no discussion of screening children either for currently needing dental procedures, or for factors that may predispose children to requiring dental procedures in the future (i.e. to be "at risk" of needing dental procedures.) Inclusion/exclusion criteria in study SR 2-07 appear to allow the participation of children irrespective of whether they meet this disorder or condition requirement. Therefore, this pharmacokinetic study does not fulfill the requirements for approval as a minor increase over minimal risk (21 CFR 50.53), because the protocol does not require that enrolled children have a disorder or condition that is the object of the research.

Finally, study SR 2-07 was not referred by an institutional review board for Federal panel review. Therefore, this protocol was not reviewed under 21 CFR 50.54. Because study SR 2-07 was not approvable under FDA regulations at 21 CFR 50.51, 21 CFR 50.52, or 21 CFR 50.53 and was not reviewed under 21 CFR 50.54, we conclude that study SR 2-07 was conducted in violation of FDA regulations for the Additional Safeguards for Children in Clinical Investigations found at 21 CFR 50 subpart D.

Question

The Division requests our assistance with determining whether the data from the pediatric pharmacokinetic study SR 2-07 should be accepted by the Agency.

Reviewer's Response and Recommendations

When a study is not conducted in accordance with FDA regulations, the Agency has the option of refusing to accept the data in support of a new drug application. Taking this step would mean that

these pharmacokinetic data to support pediatric use of the product would not be available to include in the review. The absence of this information may undermine the approvability of the product in some or all segments of the pediatric population. If so, the Agency would require the Sponsor under the Pediatric Research Equity Act to perform another pediatric study to obtain the necessary pharmacokinetic data in an appropriately selected pediatric population. While this approach may reinforce the need to comply with Agency regulations on the appropriate inclusion of children in clinical trials, it raises other ethical concerns.

The ethical basis for performing studies in children begins with the principle that the data obtained in such studies are scientifically necessary to answer a question that is important to the health and well-being of children. Obtaining information that would inform the choice of a safe and effective pediatric dose of a product that may be approved for use in the pediatric population is an important question. The clear corollary to this principle is that duplicative pediatric studies are ethically problematic, because by definition there is no scientific need for the data.

In the current situation, data have previously been collected that would inform the pharmacokinetics and safety of this product. The Agency's refusal to accept these data would necessitate a second pediatric study that would obtain exactly the same information. The fact that the second study might enroll a more appropriate pediatric subpopulation is not a sufficient ethical justification for a duplicative study.

The Agency's refusal to accept the data from study SR 2-07 would also render the contributions of the pediatric participants meaningless to support a greater public good (i.e., approval of the product). Refusing to accept the data means that pediatric participants in SR 2-07 not only received no benefit to their own health from participating, but also would lose any opportunity for the data to benefit others.

I reviewed the IRB-approved parental permission document for this study. All of the required elements of consent under 21 CFR 50.25 were included, and the document was generally well-written. The form clearly stated that Kovacaine Mist is an experimental drug that has not been approved by FDA, that the child's participation is completely voluntary, and that children would receive no direct benefit from participating. However, it is important to note that participants were told that their participation may benefit others. "Your child will not obtain any benefit from participating in the study other than the knowledge that he/she is contributing to the body of knowledge on Kovacaine Mist that may benefit others in the future." The Agency's refusal to accept the data would render this statement false.

I share the Division's concern that pediatric participants may have been inappropriately enrolled in the study SR 2-07, and recognize the need to educate both the IRB that approved the study and the Sponsor about the disorder or condition requirement. However, a refusal to accept the data from study SR 2-07 would serve the interests of neither the pediatric participants that participated in the study nor the pediatric participants that would be needed in a duplicative study. Therefore, the data from study SR 2-07 should be accepted, but the Agency should pursue other avenues of educating the IRB, the Sponsor, and the public about the situation. The team will review the Sponsor's submission in response to the Information Request and provide a follow-up consultation with respect to this issue.

Thank you for the opportunity to comment on this submission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHELLE ROTH-CLINE
03/03/2016

ROBERT M NELSON
03/03/2016

HUMAN FACTORS PROTOCOL AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 19, 2015
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208032
Product Name and Strength:	Kovanaze (tetracaine and oxymetazoline) Nasal Spray 3 %/0.05 %
Product Type:	Multi-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	St. Renatus, LLC
Submission Date:	May 29, 2015
OSE RCM #:	2015-1589
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD
Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

St. Renatus submitted a new drug application for Kovanaze (tetracaine and oxymetazoline), a nasal spray product intended to produce regional anesthesia prior to performing a restorative procedure. To ensure the product can be used safely and effectively, St. Renatus conducted a Human Factors (HF) validation study. Therefore, the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the Human Factors study results for this product to determine if they are acceptable and demonstrate that intended users can use the product safely and effectively for intended uses and environments.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Human Factors Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A B
Human Factors Study	C
Information Request	D
FDA Adverse Event Reporting System (FAERS)*	N/A E
Clinical Study Report SR-304	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Kovanaze is a nasal spray anesthetic agent used by dentists in dental restorative procedures. It will be used to produce anesthesia for the upper front teeth during procedures such as filling cavities, and it is indicated for children (b) (4) to adults. The same nasal syringe will be used in both pediatric patients and adult patients. However, the dosing of the product differs between adults and children (b) (4). (b) (4) The (b) (4) carton (b) (4) is packaged with Instructions for Use (IFU) that provides dosage and administration instructions (b) (4)

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(b) (4) (b) (4)

Other Considerations:

As part of selecting the correct dose the dental professional needs the patient's (b) (4) weight. Initially, St. Renatus expressed the weight requirements to select the correct dose in kilograms. However, based on feedback in their formative study for the (b) (4) (b) (4)

(b) (4)

(b) (4) It is recommended that all information should be presented in metric system measurements to avoid potential confusion. We provide a recommendation in Section 4.1 to address this.

We also identified additional deficiencies in the IFU and carton labeling. The (b) (4) IFU does not have a basic table to indicate the dose and number of sprays required for the adult dose. (b) (4)

(b) (4)

(b) (4) We provide our recommendations in Section 4.1. We determined these recommendations will not require further validation in another HF study.

4 CONCLUSION & RECOMMENDATIONS

Overall, we find the results of the HF validation studies acceptable; however, there is one area of deficiency we identified regarding the angle of spray administration that can be addressed through further labeling intervention. We determined that the (b) (4) IFU, carton labeling, and outer shipping box labeling can also be improved for clarity of important information. We provide recommendations in Section 4.1. These recommended changes will not require further validation through another HF study.

(b) (4)

[3] http://www.aapd.org/media/policies_guidelines/rs_commonmeds.pdf. Accessed on August 25, 2015

4.1 RECOMMENDATIONS FOR THE ST. RENATUS

A. Instructions for Use (IFU)

a. [redacted]

1. As a reference to dental professionals, add brief dosing instructions in the [redacted] IFU, i.e., 2 sprayers with an optional third dose, at the beginning of the IFU [redacted]

The [redacted] information was included in the integrated IFU that was tested, but this information is not included in the new, [redacted] IFU. This information is a helpful reference to dental professionals, and the addition of this information would not require further validation testing for the [redacted] IFU.

[redacted]

3. In the [redacted] IFU, revise the following statements in the instructions for the spray positions located just before step 1a from "Spray Position 1 (Approximately Horizontal)…" and Spray Position 2 (Approximately 45 Degree Angle)…" to read "Spray Position for First Spray (Approximately Horizontal)…" and "Spray position for second spray (Approximately 45 Degree Angle)…" This revision may provide clarity for dental professionals and would not require further validation testing for the [redacted] IFU.

[redacted]

[4] http://www.aapd.org/media/policies_guidelines/rs_commonmeds.pdf. Accessed on August 25, 2015

[5] http://www.aapd.org/media/Policies_Guidelines/G_LocalAnesthesia.pdf. Accessed on October 1, 2015

[redacted] we recommend the weight be expressed in kilograms. This revision may mitigate the risk for dosing errors and would not require further validation testing for the [redacted] IFU.

B. Carton Labeling and Outer Shipping Box Labeling

a. [redacted] Cartons

1. Submit carton labeling with the updated NDC numbers for the [redacted] cartons. The middle digits (-XXX-) are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 666, 667, and 668). The similarity of the product code numbers has led to selecting and ordering of the wrong strength and wrong drug. If the middle three digits are the same or similar, we request that you revise these numbers to ensure they are different, e.g. -668- and -213-.[6]

2. [redacted] Cartons, and the outer shipping box labels, revise and bold the statement "**Must be refrigerated, store at 2°C-8°C (36°C-46°F)**". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

[redacted]

[6] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

4.2 RECOMMENDATIONS FOR DIVISION OF ANALGESIA, ANESTHESIA, AND ADDICTION PRODUCTS (DAAAP)

A. Highlights of Prescribing Information, Dosage and Administration Section and Full Prescribing Information, Dosage and Administration Section

1. We recommend replacing the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.

2. Wherever the weight of the patient is being presented to determine dose, (b) (4) include the weight in kilograms to mitigate dosing errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

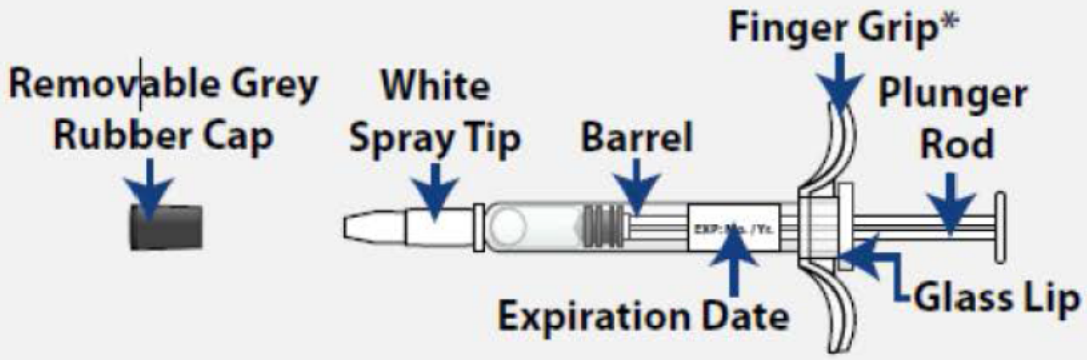
1. Table 2 presents relevant product information for Kovanaze that St. Renatus submitted on May 29, 2015.

Table 2. Relevant Product Information for Kovanaze

Initial Approval Date	N/A
Active Ingredient	Tetracaine and Oxymetazoline
Indication	Local anesthetic with a vasoconstrictor indicated for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J
Route of Administration	Intranasal
Dosage Form	Nasal Spray
Strength	3%/0.05%
Dose and Frequency	<table><tr><th>Age Group</th><th>Dose</th></tr><tr><td rowspan="2">Adults (≥ 18 years old)</td><td>2 sprays (0.2 mL per spray), 4-5 minutes apart</td></tr><tr><td>1 additional spray (0.2 mL) if adequate anesthesia has not been achieved 10 minutes after the second spray</td></tr><tr><td>Children ((b) (4) weighing ≥ 40 kg)</td><td>2 sprays (0.2 mL per spray) (b) (4) (b) (4)</td></tr></table>
How Supplied	Nasal Sprayer in a pre-filled, single use sprayer that delivers 0.2 mL per sprayer. Sprayers come in Box of 30 (b) (4) (b) (4) .
Storage	Store between 2 to 8° C - refrigerated
Container Closure	Each nasal sprayer (b) (4) When the plunger rod is suppressed, the medication is released in a plume into the nose. (b) (4) (b) (4)

Understanding the Prefilled Sprayer Parts

Assembled Prefilled Sprayer Example:



*__NOTE:__ *The Finger Grip comes separately and must be attached prior to dosing.*

(b) (4)

2. Side by Side Comparison of the Packaging, Dosing and IFU validated in the Summative Study versus the Proposed Packaging submitted on May 29, 2015.

Kovanaze (tetracaine and oxymetazoline) 0.3% and 0.05% Nasal Spray	Product Characteristics of Validated IFU Validation Study Conducted on March 31, 2015 and submitted on May 29, 2015	Product Characteristics based on May 29, 2015 submission
• Age Cohorts	• Adults 18 years and older (b) (4)	• Adults 18 years or older • Children (b) (4) weighing 40 or more kg (b) (4)
• Dose	• Adults 18 and older 2 sprays (0.2 mL) with 3rd if needed (b) (4)	• Adults 18 years or older 2 sprays (0.2 mL) with 3rd if needed • Children (b) (4) weighing 40 or more kg 2 sprays (0.2 mL) only (b) (4)
Dosage Form and Strength	0.3% and 0.05% Nasal Spray 0.2 mL per spray	0.3% and 0.05% Nasal Spray 0.2 mL per spray
How Supplied	(b) (4)	Box of 30 sprayers (b) (4) (b) (4)

APPENDIX C. HUMAN FACTORS STUDIES

C.1 Study Design for the Human Factors Validation Test Report (Adult and Pediatric), Prepared March 31, 2015 and Submitted on May 29, 2015

Table C.1.1

Study Group	Number	Type of training
Trained (Total n=30)	Dentists (n =15) Dental Assistant (n =8) Dental Hygienist (n =7)	Received training from a St. Renatus staff member. Each Participant had no prior experience with the sprayer device
Untrained (Total n=15)	Dentists (n=5) Dental Assistant (n=5) Dental Hygienist (n=5)	Participants were given one hour to self-train. Users could review the IFU, and perform a practice spray(s). Each Participant had no prior experience with the sprayer device

C.2 Results for Human Factors Validation Test Report (Adult (b) (4) Prepared March 31, 2015 and Submitted on May 29, 2015

Simulation Testing

There were 2 procedural failures during simulation testing:

1. An Untrained dental assistant who did not sit the patient upright before administering a spray.
2. An Untrained dental assistant administered only 1 spray to a 17 year old when 2 sprays were required.

Knowledge Probe

There were 11 incorrect answers with the knowledge probe questions out of a total of 540 questions asked to all participants (11/540 = 2%).

1. Failure to identify number of sprayers to administer to a 10 year old (only 1 spray); n=3
2. Failure to identify that a 17 year old should not receive a third spray; n =3
3. Failure to state correct angle for 10 years old patient; n=3
4. Failure to know maximum period of time drug may be left at room temperature (5 days); n=2

C.3 Study Design for the Human Factors Validation Test Report (Pediatric), Prepared June 29, 2015 and Submitted on August 5, 2015

Table C.3.1

Study Group	Number	Type of training
Untrained (Total n=15)	Dentists (n= 5) Dental Assistant (n=5) Dental Hygienist (n=5)	Participants were asked to select the (b) (4) Packaging when (b) (4) were placed in front of them. After those participants were given time to self-train. Users could review the Instructions for Use (IFU), and perform a practice spray(s). Each Participant had no prior experience with the sprayer device

Three scenarios for each dose cohort. Each participant did 2 scenarios and each participant was required to use a (b) (4) in at least one scenario

C.4 Results for the Human Factors Validation Test Report ((b) (4)), Prepared June 29, 2015 and Submitted on August 5, 2015

Simulation Testing

- 15/15 selected the (b) (4)
- 15/15 selected the proper supplies and correct number of sprayers based on their dose scenario
- 15/15 correctly responded to the knowledge probe questions
- 13/15 could verbalize and demonstrate the intended procedure for 30 dose scenarios

Procedural failure #1

A hygienist incorrectly stated that that both sprays should be administered at 45 degrees rather than one at 90 degrees (Image 1) and one at 45 degrees (Image 2).

Procedural failure #1 Root Cause:

Moderator: Read this set of instructions (main dosing table) and tell me what angles it says.
P9 – "The angle of the 2nd spray is 45 degrees and the angle of the first spray is horizontal."

Q to Participant: Why do you think you said 45 degrees for both sprays?
P9 – "Because of the (b) (4) I probably should have read it again."

Q to Participant: Did you read these whole sections?
P9 – "I did."

Q to Participant: Did you read these for all patient groups?
P9 – "Yea, I was just over confident."

Q to Participant: Do the instructions clearly communicate for this group that the sprays are 90 and 45 degrees?
P9 – "They do. I think I just, I should've went back to the instructions I should've read them more than once."

Q to Participant: On the back of the instructions, do you remember these sections that talk about the angles?

P9 – "Yes. I think just separated it with the (b) (4). They are pretty clear."

Q to Participant: Do you have any suggestions for changing the instructions?
P9 – "No."

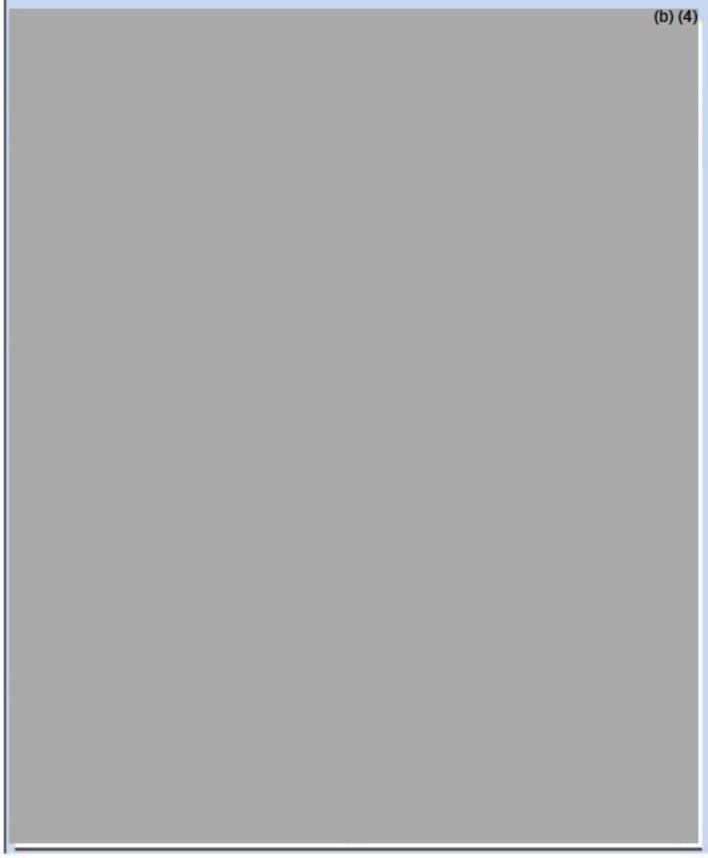
Root Cause: The participant relied on her own interpretation of the procedure and did not use the main dosing table to see that the first spray is horizontal and the second spray is at a 45 degree angle.

IAA Commentary: The participant admitted she was over confident and misinterpreted the angles. P9 stated the instructions clearly outline the required angles for this patient.

Keep in mind this failure was a secondary focus for this study. The main focus of the study was associated with the (b) (4) labeling and whether or not users could identify the dosing regimen and select the proper supplies for the patient. P9 clearly showed she could select the correct supplies and use (b) (4) in the manner intended.

Though the study required participants to verbalize the procedure, this makes it harder for some participants to do, and was a secondary focus of the study. The (b) (4) validation study for this product proved that users know that for 2 sprays one must be at a horizontal angle and one must be at the 45 degree angle. P9 relied on her memory and her interpretation of the instructions, ignoring the multiple instances where the IFU states to administer the first spray at a horizontal angle.

Mitigation Response: No mitigation is required. The IFU clearly presents the need to administer the first spray at a horizontal angle and the second spray at a 45 degree angle in 5 different places throughout the IFU as shown below.



Procedural Failure #2

One participant incorrectly answered that you only needed to wait 4 minutes after the second spray.

Procedural Failure #2 Root Cause

The Applicant's risk analysis considers this a low risk event.

Applicant's rationale In the real world had this happened this would have resulted in no harm to the patient as they are likely already numb from receiving both sprays and having waited 40% of the time required after the second spray. They would also be tested for numbness prior to procedure.

D. Information Request Responses Submitted on July 31, 2105

FDA comments are listed below in boldface and applicant responses are provided in normal font. Please note that the responses are provided in the reversed order of Questions 3, 2, and 1.

(b) (4)

Table 1: Proposed Kovanaze™ Dosing Instructions

Age Group	Dose
Adults (≥ 18 years old)	2 sprays (0.2 mL per spray), 4-5 minutes apart
	1 additional spray (0.2 mL) if adequate anesthesia has not been achieved 10 minutes after the second spray
Children (b) (4) weighing ≥ 40 kg)	2 sprays (0.2 mL per spray), (b) (4)
(b) (4)	

(b) (4)

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/s/

JAMES H SCHLICK
11/19/2015

BRENDA V BORDERS-HEMPHILL
11/19/2015

IRENE Z CHAN
11/23/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 208032

Application Type: New NDA

Name of Drug/Dosage Form: Kovanaze (tetracaine HCl, 3% w/v, and oxymetazoline HCl, 0.05% w/v) Nasal Spray

Applicant: St. Renatus

Receipt Date: May 29, 2015

Goal Date: March 29, 2016

1. Regulatory History and Applicant's Main Proposals

This is indicated for regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J. Referenced IND is 070868. PIND meeting was held on June 6, 2005; EOP 2 Meeting on March 3, 2011, and Pre-NDA meeting on August 21, 2014.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 1, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

Selected Requirements of Prescribing Information

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Name of drug product not in upper case letters*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Sections 8(subsection 8.1, 8.2, 8.3) and Section 12 (submsection 12.2) needs to be fixed*

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *Cross-references to the section not subsection as noted above.*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAVIS Y DARKWAH
08/14/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208032 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Kovanaze Established/Proper Name: Tetracaine HCl & Oxymetazoline HCl Dosage Form: nasal spray Strengths: 6 mg tetracaine HCl and 0.1 mg oxymetazoline HCl in each 0.2 mL spray. (b) (4)		
Applicant: St. Renatus Agent for Applicant (if applicable):		
Date of Application: 5/29/15 Date of Receipt: 5/29/15 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 3/29/16	Action Goal Date (if different):	
Filing Date: 7/28/15	Date of Filing Meeting: 7/16/15	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☒ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): regional anesthesia when performing a restorative procedure on teeth 4-13 and A-J		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 070868	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☒	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☐		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	It is in PLLR
Has a review of the available pregnancy and lactation data been included?	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** March 3, 2011 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 21, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 16, 2015

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mavis Darkwah	Y
	CPMS/TL:	Matt Sullivan	Y
Cross-Discipline Team Leader (CDTL)	Rigo Roca		Y
Division Director/Deputy	Sharon Hertz		Y
Office Director/Deputy			
Clinical	Reviewer:	Amelia Luckett	Y
	TL:	Rigo Roca	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Yun Xu	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	James Travis	Y
	TL:	Freda Cooner	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alex Xu	Y
	TL:	Jay Chang	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Ciby Abraham	Y
	RBPM:	Steve Kinsley	Y
• Drug Substance	Reviewer:	Debasis Ghosh/Donna Christner	
• Drug Product	Reviewer:	Xiaobin Shen/Julia Pinto	
• Process	Reviewer:	Nallaperumal Chidambaram	
• Microbiology	Reviewer:	Nallaperumal Chidambaram	
• Facility	Reviewer:	Mahesh Ramanadham	
• Biopharmaceutics	Reviewer:	Vidula Kolhatkar/Tapash Ghosh	
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	(none)	
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Koung Lee	
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Jim Schlick	
	TL:	Vicky Borders-Hemphill	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	John Lee	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO Reference to final OTC monograph for oxymetazoline. No bridge needed.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**: lack of human factors study supporting safe use in the pediatric population.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: confirm that 505(b)(2) references that the sponsor initially included were not actually needed. Sponsor has since confirmed that no listed products are referenced for this NDA, only the final monograph. They have revised their 356(h) to reflect this.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sharon Hertz **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW W SULLIVAN
07/22/2015