CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208032Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

Recommendation:
NDA: Approval

NDA 208032
Review #1
Review Date: 6/17/16

Drug Name/Dosage Form	Tetracaine HCl and Oxymetazoline HCl Spray
Strength	3%/0.05%
Route of Administration	Nasal
Rx/OTC Dispensed	Rx
Applicant	St. Renatus, LLC
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original Submission	5/29/15
eCTD 10	10/1/15
eCTD 15	11/5/15
eCTD 16	12/7/15
eCTD 21	2/16/16
eCTD 22	2/17/16

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION
Drug Substance	Debasis Ghosh	ONDP
Drug Product	Xiaobin Shen	ONDP
Process	Erin Kim	OPF
Microbiology	Denise Miller	OPF
Facility	Ebern Dobbin	OPF
Biopharmaceutics	Vidula Kolhatkar	ONDP
Project/Business Process Manager	Steven Kinsley	OPRO
Application Technical Lead	Ciby Abraham	ONDP

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Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505b2**

2. **CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH OC	Pending	Post Approval inspection		

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the recommendations from drug substance, drug product, biopharmaceutics, microbiology, process, and the office of compliance, we recommend approval of Kovanaze 3% Tetracaine HCl/0.05% Oxymetazoline HCl nasal spray from a Chemistry, Manufacturing, and Control (CMC) perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

A. Description of the Product

The drug substance, Tetracaine HCl is manufactured by [redacted] (b) (4) and is referenced in DMF# [redacted] (b) (4) (adequate, last reviewed 12/1/2015). Tetracaine HCl is a white crystalline powder that is freely soluble in water. [redacted] (b) (4)

The drug substance, Oxymetazoline HCl is manufactured by [redacted] (b) (4) [redacted] (b) (4), and is referenced in DMF# [redacted] (b) (4) (adequate, last reviewed 11/24/2015). Oxymetazoline HCl is a white or almost white crystalline powder with a slight odor that is freely soluble in water. [redacted] (b) (4)

The drug product, Kovanaze Nasal Spray (tetracaine hydrochloride, 3% w/v, and oxymetazoline hydrochloride, 0.05% w/v) consists of a [redacted] (b) (4) aqueous solution of two drug substances, filled in unit-dose Accuspray nasal spray systems. For adults, the total deliverable volume of 0.2 mL per sprayer unit is dispensed as a single spray of 0.2 mL administered in the nostril ipsilateral to the tooth [redacted] (b) (4) [redacted] (b) (4) The spray from one sprayer unit delivers 6 mg tetracaine HCl and 0.1 mg oxymetazoline HCl. [redacted] (b) (4)

(b) (4)

(b) (4) Based on the stability data reported by the applicant, 15 month expiry will be granted for the drug product at controlled cold temperatures between 2°C and 8°C with excursions between 0°C and 15°C.

B. Description of How the Drug Product is Intended to be Used

Kovanaze 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).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate information in the manufacturing and controls in the areas of drug substance, drug product, process, microbiology, facilities, and biopharmaceutics. CMC is recommending the approval of Kovanaze Nasal spray.

Executive Risk Assessment Summary

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	H	-	Acceptable	Stability: The drug product is granted a (b) (4) month expiry at (b) (4)°C. No increasing trends in impurity were identified.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-
Content uniformity	• Formulation • Raw materials • Process	L	-	-	-

	parameters • Scale/equipment • Site				
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.
Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

(b) (4)

[redacted]

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R.2 Comparability Protocols

(b) (4)

[redacted]

(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

There are no Biopharmaceutics data to review in this application.

Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
01/26/16

QUALITY ASSESSMENT
NDA # 208032

Supervisor Comments and Concurrence:

I concur that there is no Biopharmaceutics information to review in this application.

Kelly Kitchens, Ph.D.
Quality Assessment Lead (Acting), Branch II
Division of Biopharmaceutics/ONDP
01/26/16

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF MICROBIOLOGY

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

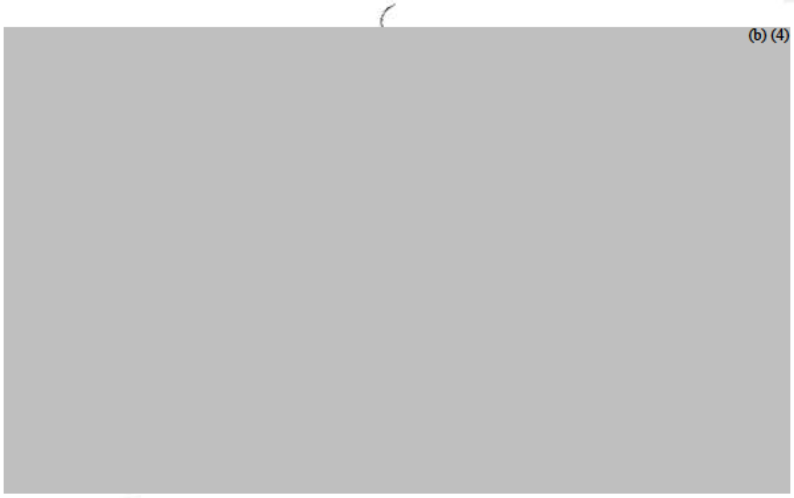
P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – Kovanze Nasal Spray is a (b) (4) aqueous solution filled in a unit-dose Accuspray™ nasal spray system filled with a deliverable volume of 0.2 mL per sprayer unit. Adults may be administered up to three units and pediatric patients can receive (b) (4) two sprays (b) (4)
- Drug product composition – The composition was provided in Table 3.2.P.1.1. The solution with the two active ingredients is (b) (4) with citric acid and sodium citrate and (b) (4) with benzyl alcohol. A (b) (4) hydroxyethylcellulose is also included.
- Description of container closure system – The container closure is the Accuspray nasal spray unit manufactured by BD Medical. The system (b) (4)

Figure 1 Illustration of Accuspray™ Sprayer

(b) (4)



P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – NA

(b) (4)

- Justification for not having a microbial limit specification for a non-sterile drug product – NA, product has a microbial limit specification.

-ADEQUATE-

REVIEWER COMMENT – The proposed drug product is adequately preserved.

P.3 Manufacture

P.3.1 Manufacturers

P.3.3 Description of the Manufacturing Process and Process Controls

This is a non-sterile drug product. The product is formulated and (b) (4) (b) (4) (b) (4) Storage is at 2-8°C.

P.5 Control of Drug Product

P.5.1 Specifications

P.5.2 Analytical Procedures

- Endotoxin – NA
- Sterility – NA
- Microbial Limits Test (MLT) – Microbial limits tests are proposed for release following USP <61> and <62>. The proposed limits are as follows:
  - TAMC: Not more than (b) (4) cfu/unit
  - TYMC: Not more than cfu/unit
  - Absence of the following:
    - *P. aeruginosa*
    - *S. aureus*

Reviewer Comment: The proposed release specifications did not include the absence of *Burkholderia cepacia*. As this is an aqueous non-sterile product, this test is recommended for release. An information request was sent on 21 August 2015 requesting this additional testing. The sponsor responded on 05 November 2015 and agreed to add this test to the release testing. The sponsor also submitted a risk assessment and method validation for the *B. cepacia*

Review of Response: A risk assessment was conducted to include the raw materials used and the manufacturing processes for each facility. The assessment concluded that the risk of *B. cepacia* contamination to be very low. This reviewer agrees with the assessment that the risk for *B. cepacia* contamination to the product is low.

The *B. cepacia* testing for the product will be tested following the methods in UPS <62> and using an enrichment in Tryptone Azelastine Tween Broth (TAT) and plating on Oxidation/Fermentation-Polymyxin-Bacitracin-Lactose Agar (OFPBL). The incubation conditions are30-35°C. The method suitability included two different *B. cepacia* strains from ATCC and a *B. cepacia* isolate from environmental monitoring. The method suitability is supportive of testing ability to detect this contamination.

Note: The sponsor proposes skip lot testing for microbial limits after three validation lots for each manufacturing site met the acceptance criteria. Skip lot testing is proposed by ICH Guidance 6A Decision Tree #8. The rational for skip lot testing includes the following:

- All of the MLT testing performed to date has met the acceptance criteria.
- The AET data provided supports the effectiveness (b) (4)
- This is a topical product that is not applied to wounds and therefore presents a low patient risk.

There are no microbial quality concerns for skip lot testing for this product.

-ADEQUATE-

REVIEWER COMMENT – The proposed release specifications are acceptable.

P.7 Container Closure System - NA

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

Long Term: 5°C

Microbial Limits performed at 0, 12, and 24 months

Accelerated: 25°C/60%RH

Microbial Limits performed at 0, and 6 months

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The sponsor will complete the stability testing for the lots currently on stability. After approval, one lot from each manufacturing site will be added annually to the stability program. Results will be submitted in annual reports and any batch failing to meet approved specification will be withdrawn from the market unless the deviation does not affect the safety and efficacy of the product. The sponsor will discuss the matter with the appropriate Review Division and provide justification for the batch to remain on the market.

- Container Closure Integrity – NA
- Endotoxin – NA
- Microbial Limits – To be tested at 0 and 24 months under the long term storage conditions (5°C)

P.8.3 Stability Data

Four pilot scale lots manufactured at (b) (4) were placed on stability and one lot manufactured at (b) (4) All of the manufactured lots completed up to 24 months with three lots completing 30 months. The (b) (4) lot completed through 12 months. All lots met the specifications for microbial limits.

-ADEQUATE-

REVIEWER COMMENT – The stability program is acceptable.

A APPENDICES - NA

R REGIONAL INFORMATION

R.1 Executed Batch Record - NA

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT - NA

Reviewer's Assessment and Signature: There were no quality microbiology deficiencies noted in the information provided.
Recommendation: Approve from a quality microbiology perspective.

Denise A. Miller
Microbiologist, OPF/DMA Branch II

Supervisor Comments and Concurrence:
I concur with the Product Quality Microbiology assessment and approval recommendation.

Neal J. Sweeney, Ph.D.
Quality Assessment Lead (Acting)
OPQ/OPF/DMA/Branch II

Note: additional reviewers can be added, as appropriate

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling, Package Insert, and Carton – Currently being evaluated due to the extension of the PDUFA clock.

II. Administrative

A. Reviewer's Signature

Ciby J. Abraham -A

Digitally signed by Ciby J. Abraham -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000827346, cn=Ciby J. Abraham -A
Date: 2016.06.20 15:20:32 -04'00'

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
Application Technical Lead
ONDP/DIVII/Branch IV