CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211321Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR EVALUATION OF DRUGS

Memorandum

DATE: May 14, 2019

TO: Division of Neurology Products

FROM: Wendy I. Wilson-Lee, Ph.D.
Branch Chief, OPQ/ONDP

SUBJECT: OPQ Review Memo

APPLICATION/DRUG: NDA 211321 Resub 24 Midazolam Nasal Spray

OPQ recommends approval of NDA 211321 based on our approval recommendation from the first review cycle (see OPQ Integrated Quality Assessment dated March 29, 2019). No new CMC information was provided in the resubmission. All facilities remain in good standing. The overall manufacturing inspection recommendation from CDER is approve (OMIR date May 14, 2019).

Wendy
Wilson- Lee

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Recommendation: APPROVAL

NDA 211321
Review # 01

Drug Name/Dosage Form	Midazolam Spray
Strength	5 mg
Route of Administration	Nasal
Rx/OTC Dispensed	Rx
Applicant	Proximagen, LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	29-MAY-2018	*Amendment*	21-DEC-2018
Amendment	28-SEP-2018	*Amendment*	07-JAN-2019
Amendment	11-OCT-2018	*Amendment*	28-JAN-2019
Amendment	26-NOV-2018	*Amendment*	01-FEB-2019
Amendment	29-NOV-2018	*Amendment*	28-MAR-2019
Amendment	17-DEC-2018	*Amendment*	29-MAR-2019
Amendment	20-DEC-2018		

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Ben Zhang	Suong Tran	ONDP
Drug Product	Stephanie Emory	Wendy Wilson-Lee	
Environmental			
Labeling			
Manufacturing	Tianhong Tim Zhou	Nallaperumal Chidambaram	OPF
Microbiology	Eric Adeeku	Jesse Wells	
Biopharmaceutics	Mei Ou	Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Dahlia Walters		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	09-JAN-2019	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77421	Midazolam Spray Solution
NDA	18654	Midazolam HCl Injection (withdrawn)
ANDA	75857	Midazolam HCl Injection

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH – device	Complete	Approve	14-MAR-2014	Matthew Ondeck
CDRH – compliance	Complete	Not approvable	29-MAR-2019	Matthew Ondeck

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 211321 for Midazolam Nasal Spray, 5 mg.

II. Summary of Quality Assessments

A. Product Overview

The proposed product is a drug device combination product consisting of midazolam formulated for nasal administration via a portable single-use (unit dose) delivery system via spray pump. The solution is a non-preserved, clear, colorless to yellowish solution essentially free from visible particulate matter packaged in a (b) (4) glass vial stoppered with (b) (4) rubber plunger. Each dose contains 5 mg of midazolam in 0.1 mL of nasal spray. Assembled device is further packaged in a single blister with a peel off lid. Midazolam nasal spray was granted Fast Track designation (October 2008) and Orphan Drug designation (October 2009). The rationale of selecting a nasal spray for emergency use is to meet both patient and caregiver requirement since the treatment will be hand held and portable.

Proposed Indication(s) including Intended Patient Population	***Treatment of seizures in patients 12 years of age or older who require control of intermittent episodes of increased seizure activity (e.g. seizure clusters, acute repetitive seizures)***
Duration of Treatment	***Intermittent, chronic***
Maximum Daily Dose	***10 mg***
Alternative Methods of Administration	***None***

B. Quality Assessment Overview

Midazolam is a white to yellowish, crystalline powder. It has no chiral center and no optical activity. It is practically insoluble in water, soluble in acetone, methanol and ethanol. There are no known polymorphs of midazolam, and it is not known to be hygroscopic. Midazolam is lipophilic at physiological pH. The applicant references DMF (b) (4) for the related information for midazolam drug substance. The DMF remains adequate to support the proposed product. The applicant provided the drug substance specification and batch analysis data for four commercial batches of midazolam in the NDA. The results confirm that the midazolam drug substance from the proposed commercial supplier is of suitable quality for commercialization.

Formulation development focused on (b) (4). The solution is supplied in a (b) (4) glass vial with rubber stopper, (b) (4) in a single-use nasal spray device, packaged individually in a blister pack. The potential for particulate matter contamination and delamination is considered low risk as the delivery vehicle is a combination (b) (4). All excipients are compendial, though MPEG (b) (4) is novel for the intranasal route of administration. Use of MPEG (b) (4) for the new route of administration is supported by a nonclinical data in two species, as confirmed by the nonclinical team. No additional controls are needed.

The primary container and device are constructed of commonly used materials for nasal spray products. Each device delivers one spray containing 5 mg midazolam. The drug product, vials, and device were appropriately evaluated for elemental impurities and extractables/leachables. No significant risks were identified. The fill volume (label claim) is (b) (4) mL ((b) (4) g) with an overfill ((b) (4) mL) (b) (4).

The product is controlled by a combination of tests performed on the filled vials and pre-assembled devices. Drug-product specific impurities have been adequately identified and characterized. (b) (4) testing demonstrated that (b) (4) is important for product stability. The assay/impurities test method has been revised with better control of (b) (4) for analytical samples during extraction from the vial.

Primary stability data is provided up to 31 months. However, a shorter expiry was proposed based on increasing degradant levels on stability, some of which approach their respective limits at 31 months for at least one registration batch. **The proposed** (b) (4) **month expiry under room temperature storage conditions is granted.**

The manufacturing process involves (b) (4). To ensure the accurate delivery of 5 mg dose in each 100 µL spray, the applicant conducted extensive process qualification studies (b) (4). The CPP and acceptance limits have been finalized considering the manufacturing process capability.

Throughout the clinical development and process development, the applicant manufactured numerous batches at the proposed commercial scale (b) (4) kg and tested for in process attributes/finished product Critical quality attributes (CQA) to be well within acceptance limits and release specifications. There will not be any scale up challenges since the registration batch and the proposed commercial batches will have the same batch size of (b) (4) kg.

(b) (4)
, request for information were issued (b) (4)
in viscosity determinant formulation ingredient. Information Request was also issued to address Residual risk in demonstrating compatibility between bulk drug product and the manufacturing equipment contact surface related potential extractable and leachable. Upon request for information, the applicant provided supportive data covering possible variation in viscosity of the compendia grade excipients and concluded the drug product could accommodate the change without impacting performance. The applicant also adequately addressed the extractable/leachable risk from the equipment contact surface.

This is a non-sterile nasal spray that contains no preservatives. The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> and <62>. The Microbial Limits acceptance criteria are also consistent with USP Chapter <1111>. The product is also tested to ensure the absence of *Burkholderia cepacia* complex (BCC), *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

A detailed review by the Division of Biopharmaceutics is not needed for this NDA based on the proposed dosage form and no relevant Biopharmaceutics issues that need to be addressed. The proposed drug product is a solution for single use. Dissolution is not proposed or required as part of drug product QC specifications. The pivotal BA/BE study (MZ0714) comparing the proposed drug product with the Reference Standard (RS) product (midazolam HCL sterile injection, ANDA 075857 by Hospira).

All optimized formulations (12.5, 25, 50 and 75 mg/mL) during the pharmaceutical development have been used in Phase 1 and 3 clinical studies. The 50 mg/mL formulation is the same as the proposed to-be-marketed formulation. In addition, there are no changes of (i) manufacturing process, (ii) manufacturing site, and (iii) the nasal spray nit device from the Phase 3 clinical formulation and the proposed commercial formulation.

From a CDER perspective, all facilities are acceptable for the operations listed in NDA 211321. The OPF assessment evaluated facilities associated with the drug constituent part of this combination product. CDER defers to CDRH for evaluation of the acceptability of facilities associated with the device constituent part.

The claim for categorical exclusion is granted in accordance with 21 CFR 25.15(d) and 25.31(b).

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment

APPEARS THIS WAY ON ORIGINAL

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation Container Closure Raw Materials Process Scale Equipment Site	**Low**	(b) (4)	**Acceptable**	
Physical Stability		**Low**		**Acceptable**	
Particulate Matter		**Medium**		**Acceptable**	
Microbial Limits		**Low**		**Acceptable**	
Leachables		**Medium**		**Acceptable**	
pH		**Low**		**Acceptable**	
(b) (4)		**Low**		**Acceptable**	
Viscosity		**Low**		**Acceptable**	
Fill Volume		**Low**		**Acceptable**	
Droplet Size Distribution		**High**		**Acceptable**	
Actuation Force		**Medium**		**Acceptable**	
Spray Pattern		**High**		**Acceptable**	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Content Uniformity of Spray		**Medium**	(b) (4)	**Acceptable**	
Delivered Dose		**Medium**		**Acceptable**	
Weight Loss		**Medium**		**Acceptable**	

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 28 MAR 2019

TO: NDA 211321

FROM: Stephanie Emory, OPQ Drug Product primary reviewer for NDA 211321

SUBJECT: Qualification of Degradants A & B limits, updated specification and expiry

APPLICATION/DRUG: NDA 211321, NAYZILAM™ (midazolam nasal spray), 5 mg

For the drug product specification, the applicant initially proposed an acceptance criterion of NMT (b) (4)% each for Degradant A and Degradant B, which exceed the ICH Q3B qualification threshold 0.5% based on a maximum daily dose of 10 mg for this product. However, based on a review of the Nonclinical information submitted, the proposed limits are not adequately qualified.

The applicant was informed in the information request sent March 26, 2019, that results from a 3-month toxicity study are needed in order to qualify the proposed limits. The applicant was instructed to revise the proposed limits to align with the ICH qualification limits and that, considering the revised specified degradant limits and the drug product stability data submitted, the Agency would grant an 18-month drug product expiry when stored in the commercial packaging at USP controlled room temperature, rather than the proposed (b) (4) month expiry.

In their email response received March 27, 2019, the applicant acknowledged that the 3-month toxicity study had not been conducted to qualify the proposed NMT (b) (4)% limit for each degradant. On March 28, 2019, the applicant updated the degradant limits and shelf-life as appropriate throughout the NDA.

Stephanie Emory

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Wendy Wilson- Lee

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LABELING

I. Package Inserts – submitted 29May2018

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	NAYZILAM™ (midazolam nasal spray), CIV
Dosage form, route of administration	
Controlled drug substance symbol (if applicable)	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Single-use nasal spray unit containing 5 mg midazolam per 0.1 ml solution

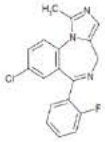
2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4)

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	NAYZILAM is supplied as a single-dose nasal spray unit containing 5 mg of midazolam in 0.1 mL solution.
Strengths: in metric system	
Active moiety expression of strength with equivalence statement (if applicable)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not applicable. Device labeling is sufficient for identification.

4. Section 11 Description

Item	Information Provided in NDA
Proprietary name and established name	NAYZILAM contains midazolam *Revise to include full established name.*
Dosage form and route of administration	No information *Revise to add dosage form and route of administration*
Active moiety expression of strength with equivalence statement (if applicable)	Each single-dose NAYZILAM unit delivers 5 mg of midazolam in 0.1 mL of solution
List inactive ingredients, by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4), (b) (4); polyethylene glycol 400 (b) (4); propylene glycol, (b) (4); ethanol, (b) (4); and purified water, (b) (4). *Revise to use the preferred name PEG-6 methyl ether, remove* (b) (4) *and list inactive ingredients in alphabetical order per USP <1091>*
Pharmacological/ therapeutic class	midazolam, a compound of the benzodiazepine class
Chemical name, structural formula, molecular weight	Midazolam is chemically designated as 8-Chloro-6-(o-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4] benzodiazepine, and it has the following structure:  The empirical formula is $C_{18}H_{13}ClFN_3$ representing a molecular weight of 325.8.
Other important chemical or physical properties (such as pKa or pH)	Midazolam, USP is a white or yellowish, crystalline powder that is practically insoluble in water, soluble in methanol, and freely soluble in acetone and in alcohol. *Revise to include drug product physical and chemical properties such as color and pH.*

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	NAYZILAM is supplied as a solution of midazolam. Each single-dose nasal spray unit delivers 5 mg of midazolam in 0.1 mL of solution.
Available units (e.g., bottles of 100 tablets)	NAYZILAM is supplied in boxes of 2 nasal spray units (NDC XXXX-XXXX-XX), each contained within an individual blister pack.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	*Update NDC #.* (b) (4)
Special handling (e.g., protect from light)	Do not open the blister packaging until ready to use.
Storage conditions	Store at controlled room temperature 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for XXX *Update manufacturer/distributor information.*

6. Medication Guide

Information Provided in NDA	
How should I store NAYZILAM?	Store NAYZILAM at room temperature, between 68°F to 77°F (20°C to 25°C). Keep NAYZILAM in the blister package until (b) (4) use.
What are the ingredients in NAYZILAM?	Active ingredient: midazolam Inactive ingredients: (b) (4); polyethylene glycol 400 (b) (4); propylene glycol, (b) (4); ethanol, (b) (4); and purified water, (b) (4) *Revise to use the preferred name PEG-6 methyl ether,* (b) (4) *and list inactive ingredients in alphabetical order per USP <1091>*
Manufactured for:	*Update manufacturer/distributor information.*

7. Instructions for Use (submitted 29May2018) – *no revisions needed*

Reviewer's Assessment of package inserts: ***Adequate, pending revisions as noted above in red***

II. Structured Product Labeling (SPL) – submitted 29May2018

NAYZILAM
midazolam spray

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:7217 (b) (4) *Update NDC#*
Route of Administration	NASAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MIDAZOLAM (UNII: R60L0SM5BC) (MIDAZOLAM - UNII:R60L0SM5BC)	MIDAZOLAM	5 mg in 0.1 mL

Inactive Ingredients

Ingredient Name (b) (4)	Strength
PEG (b) (4) METHYL ETHER (UNII: (b) (4)) *Use correct UNII code for PEG-6 methyl ether*	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
ALCOHOL (UNII: 3K9958V90M)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:7217 (b) (4) *Update NDC#*	2 in 1 CARTON		
1	*Add: NDC # for blister/device*	*Add: 1 in 1 BLISTER PACK*		
1		0.1 mL in 1 VIAL, SINGLE-DOSE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	211321		

Labeler - Proximagen, LLC (081038950) *Also list Proximagen as Registrant.*

Establishment *Include all DS and DP manufacturers.*

Name	Address	ID/FEI	Business Operations
(b) (4)			manufacture(7217 (b) (4)) , analysis(7217 (b) (4)) *Update NDC #s.*

Reviewer's Assessment of SPL: ***Adequate, pending revisions as noted above in red***

III. Labels – submitted 29May2018

1. ***Container and Carton Labels***

(b) (4)

2. ***Carton Label***

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Item	Information provided in the device labels	Information provided in the blister label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	nayzilam™ (midazolam) nasal spray 5mg [redacted] (b) (4) 1 Dose	nayzilam™ (midazolam) nasal spray 5mg Each dose contains 5 mg of midazolam in 0.1 mL of nasal spray. [redacted] (b) (4)	PDP: nayzilam™ (midazolam) nasal spray 5mg 2 Nasal Spray Units (1 dose per unit) Back Panel: Each dose contains 5 mg of midazolam in 0.1 mL of nasal spray. Each nasal spray unit contains a single dose.
Dosage strength			
Net contents			
Lot number and expiration date (21 CFR 201.17)	present	present (bottom panel)	
Storage conditions	absent	Store at controlled room temperature 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).	
Name of manufacturer/distributor	Mfd. For *Update information*	[redacted] (b) (4) manufactured for [redacted] (b) (4) *Update information.*	
Special instructions	No information	FOR NASAL USE ONLY DO NOT test or prime before use.	
"Rx only" displayed prominently on the main panel	present		
NDC number (21 CFR 207.35(b)(3)(i))	NDC XXXX-XXXX-XX *Update NDC#.* [redacted] (b) (4)		
Bar code (21CFR 201.25)	present		
Controlled substance symbol	CIV symbol		

Reviewer's Assessment of Labels: ***Adequate, pending revisions as noted above in red***

Stephanie Emory

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Wendy Wilson- Lee

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QUALITY ASSESSMENT

BIOPHARMACEUTICS

NDA: 211321 [505(b)(2)]
Drug Product Name / Strength: Nayzilam™ (Midazolam) Nasal Spray, 50 mg/mL
Route of Administration: Nasal
Applicant Name: Proximagen, LLC
Proposed Indication: Acute treatment of seizures in patients 12 years of age or older who require control of intermittent episodes of increased seizure activity (e.g. acute repetitive seizures, seizure clusters)
Submission Date: 05/29/2018
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

REVIEW SUMMARY

The proposed drug product, Nayzilam™ (Midazolam) Nasal Spray (MDZ NS), 50 mg/mL midazolam solution, is a drug-device combination product consisting of midazolam formulated for nasal administration via a portable single-use delivery system via spray pump.

The proposed drug product is a solution for single use. Dissolution is not proposed or required as part of drug product QC specifications. The pivotal BA/BE study (MZ0714) comparing the proposed drug product with the Reference Standard (RS) product (midazolam HCL sterile injection, ANDA 075857 by Hospira).

As presented in Table 1, all optimized formulations (12.5, 25, 50 and 75 mg/mL) during the pharmaceutical development have been used in Phase 1 and 3 clinical studies. The 50 mg/mL formulation is the same as the proposed to-be-marketed formulation. In addition, there are no changes of (i) manufacturing process, (ii) manufacturing site, and (iii) the nasal spray nit device from the Phase 3 clinical formulation and the proposed commercial formulation.

Table 1: Formulations during the pharmaceutical development

Original MDZ NS-ITI Formulation, used in preclinical studies	Optimized MDZ NS Formulations, used in Phase 1 and 3 studies
F01: 25 mg/mL F02: 50 mg/mL F03: 75 mg/mL F08: placebo formulation	F04: 12.5 mg/mL F05: 25 mg/mL F06: 50 mg/mL (*the proposed to-be-marketed formulation*) F07: 75 mg/mL

Excipient (% w/w)	Formulation Code & Strength							
	F01	F02	F03	F04	F05	F06	F07	F08
	25 mg/mL	50 mg/mL	75 mg/mL	12.5 mg/mL	25 mg/mL	50 mg/mL	75 mg/mL	Placebo
(b) (4) NF	(b) (4)							
PEG-400, NF								
Propylene glycol, USP								
Ethanol, (b) (4) USP[2]								
Water, USP								
Midazolam, USP								
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

[1] The formulation composition during clinical development for the manufacture of clinical and stability 50 mg/mL batches (F06) (b) (4) The proposed commercial 50 mg/mL formulation (b) (4) Refer to Module 3.2.P.2.2 for further explanation.
[2] Ethanol, (b) (4)

CONCLUSION AND RECOMMENDATION:

A detailed review by the Division of Biopharmaceutics is not needed for this NDA for Nayzilam™ (Midazolam) Nasal Spray, 5 mg/0.1 mL, considering the proposed dosage form and no relevant Biopharmaceutics issues that need to be addressed.

Mei Ou

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Ta-Chen Wu

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CHAPTER VIII: Microbiology

MICROBIOLOGY

Product Background: -

NDA: 211321

Drug Product Name / Strength: Midazolam nasal spray / 5 mg

Route of Administration: Nasal spray

Applicant's Name:

Proximagen, LLC
505 Waterford Park, Highway 169 North
Plymouth, MN 55441

Manufacturing Site: N/A

Method of Sterilization: Non-sterile

Review Recommendation:

The submission is **recommended** for approval. No outstanding issues remain.

List of Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
05/29/2018	05/29/2018	N/A	06/05/2018

Highlight Key Outstanding Issues from Last Cycle: None

Remarks:

This is an electronic submission.

Concise Description Outstanding Issues Remaining:

None

Supporting Documents:

N (b) (4) r1.doc – The (b) (4) sterility assurance review of drug product manufactured at the same manufacturing facility that was deemed approvable pending resolution of microbiological deficiencies.

N (b) (4) r2.doc – Product quality microbiology review of drug product manufactured at the same facility that was found adequate in the (b) (4) microbiology review.

List Number of Comparability Protocols (ANDAs only):

No CP was included in the application.

P.1 Description of the Composition of the Drug Product

Drug product composition –

(section 3.2.P.1).

Ingredient	Function	Composition (mg/0.1 mL)
Midazolam, USP	Drug Substance	5.00
(b) (4), NF		(b) (4)
Polyethylene glycol 400 (PEG 400), NF		
Propylene glycol, USP		
Ethanol, (b) (4) USP		
Water (b) (4)		
		(D) (4)
Total Delivered Weight		108.51

Description of container closure system –

(sections 3.2.P.3.3 and 3.2.P.7).

The drug product solution is filled into a (b) (4) glass vial sealed with a (b) (4) rubber stopper.

Component	Materials of Construction	Manufacturer Supplier
Actuator	White Body (chassis)	(b) (4)
	Spray pin	
	Cannula	
Container Holder	(b) (4)	
Glass Vial	(b) (4) Clear Tubular Glass, (b) (4)	
Stopper (Plunger)	(b) (4) Rubber, (b) (4)	

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product microbiological quality.

Adequate

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Antimicrobial Effectiveness Testing

N/A. The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

Adequate

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(b) (4)

[redacted]

P.7 Container Closure

Summary table of the container closure system proposed

See section P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(section 3.2.P.8.1).

Primary stability studies are currently in progress for 3 lots of the drug product manufactured at the intended commercial manufacturing site, using the intended commercial manufacturing process. The storage conditions are as follows:

- Long-term storage condition: 25 °C/60 % RH
- Intermediate storage condition: 30 °C/65 % RH
- Accelerated storage condition: 40 °C/75 % RH

Proposed Expiry: (b) (4) months

Adequate

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(section 3.2.P.8.2).

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Microbial Limits ❖ TAMC ❖ TYMC	USP <61>	(b) (4) ❖ ❖

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25 °C/60 % RH

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
Microbial Limits	X				X			X	X

Post Approval Stability Commitment

(section 3.2.P.8.2).

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Adequate

P.8.3 Stability Data

(section 3.2.P.8.3).
Lot numbers #300869, 300870 and 301289 met specifications for TAMC and TYMC and demonstrated the absence of *S. aureus* and *P. aeruginosa* at the 31-month time points. However, the product was not tested for the absence of *B. cepacia* during stability. The sponsor explained that *B. Cepacia* was added to the specification after testing of NDA stability batches; therefore, data are not available.

Note to Reviewer: Although the absence of *B. cepacia* was not demonstrated, the 2016 study for validation of microbial enumeration and test for specified organisms demonstrated that applicant's methods can detect *B. cepacia* (section 3.2.P.5.3). Therefore, this information will not be requested.

Adequate

R Regional Information

Executed Batch Records

(section 3.2.R).
Executed batch records for lot #301289 were included in the submission.

Adequate

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

2.A. Package Insert

(b) (4)

(section 1.14.1.2).
Storage temperature: 20 – 25 °C [68 – 77 °F] (Excursions permitted to 15 – 30 °C [59 – 86 °F]).
Route of administration: nasal spray
Container: Single dose

Adequate

Primary Microbiology Reviewer Name and Date:

Eric Adeeku, 09/19/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jesse Wells, 09/19/2018

Eric Adeeku

Digitally signed by Eric Adeeku
Date: 9/19/2018 10:40:18AM
GUID: 508da70b00028e3db199467cfbd47cb0

Jesse Wells

Digitally signed by Jesse Wells
Date: 9/19/2018 10:26:44AM
GUID: 508da70b00028ea901ac6652677f7d00

Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 3/29/2019 03:21:48PM
GUID: 50816dbc000085595ca3284bbca465a8