CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212295Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212295
Assessment 1

Drug Product Name	Remimazolam for Injection
Dosage Form	lyophilized powder for reconstitution
Strength	Remimazolam besylate (b) (4) mg to yield remimazolam free base 20 mg; when reconstituted with 8.2 ml 0.9% saline solution the concentration will be 2.5 mg/ 1 mL
Route of Administration	intravenous
Rx/OTC Dispensed	Rx
Applicant	Cosmo Technologies, Ltd.
US agent, if applicable	Conventus BioMedical Solutions, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
NDA 212295	5 Apr 2019	All
Supporting document 7; eCTD 0006	24 May 2019	Facilities
Supporting document 9; eCTD 0008	28 May 2019	Micro
Supporting document 13; eCTD 0012	1 Aug 2019	Drug substance, drug product – response to 74 day letter
Supporting document 14; eCTD 0013	5 Aug 2019	Drug product
Supporting document 16; eCTD 0015	20 Aug 2019	Drug Product
Supporting document 18; eCTD 0017	16 Sep 2019	Micro
Supporting document 20; eCTD 0019	30 Sep 2019	Drug Product
Supporting document 21; eCTD 0020	6 Sep 2019	Drug Product
Supporting document 25; eCTD 0024	15 Nov 2019	Drug Product
Supporting document 29; eCTD 0028	6 Dec 2019	Drug Product

Supporting document 30; eCTD 0029	12 Dec 2019	Drug Product
Supporting document 44; eCTD 0043	11 Feb 2020	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Joe Leginus	Donna Christner
Drug Product	Valerie Amspacher	Julia Pinto
Manufacturing	Wendy Tan	Bryan Riley
Microbiology	Vikas Moolchandani	Ubrani Venkataram
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	Dongping Dai	Jason Rodriquez
Environmental	Valerie Amspacher	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Based on a review of the submitted information and responses to IR's approval of this application is recommended.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Remimazolam for injection 20 mg drug product is a sterile, white to off-white lyophilized powder filled in single-use clear glass vials. Drug Substance and Drug Product specifications are adequate to support the safety and efficacy of commercial drug product.

We agree with the sponsor's proposed shelf-life of 36-months when stored at controlled room temperature between 20-25°C, excursions permitted between 15-30°C, and protected from light.

Proposed Indication(s)	Intravenous sedation (procedure)

including Intended Patient Population	
Duration of Treatment	(b) (4)
Maximum Daily Dose	
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Remimazolam besylate is a benzodiazepine derivative with a single chiral center, synthesized as the S enantiomer. It is isolated as the besylate salt (1:1).
Reference is made to DMF (b) (4) for information on the remimazolam besylate drug substance. DMF (b) (4) has been recently reviewed and found to be Adequate. A copy of the Letter of Authorization to allow the Agency to refer to this DMF has been provided in the NDA. Limited information for the drug substance has been provided in NDA 212295 and is summarized below.
A retest date of (b) (4) months after manufacture is granted for remimazolam besylate drug substance when stored at (b) (4) °C. This is supported by acceptable stability data provided in DMF (b) (4)

Drug Product: Adequate

The regulatory analytical procedures are appropriate for the intended use, including method validation.
Impurities are adequately controlled according to ICH Q3B guidance.
The drug product specification is adequate to assure the identity, strength, quality, purity, and potency of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy. Batch analysis is provided and meets specifications.
We agree with the sponsor's proposed shelf-life of 36-months when stored at controlled room temperature between 20-25°C, excursions permitted between 15-30°C, and protected from light.

Labeling: Adequate

Manufacturing: Adequate

The proposed commercial batch size of (b) (4) L is similar to validation batch size, hence there is no scale up. There are sufficient development studies conducted to support the proposed commercial manufacturing, the identified risks associated with the manufacturing processes are adequately mitigated, and the manufacturing processes are clearly

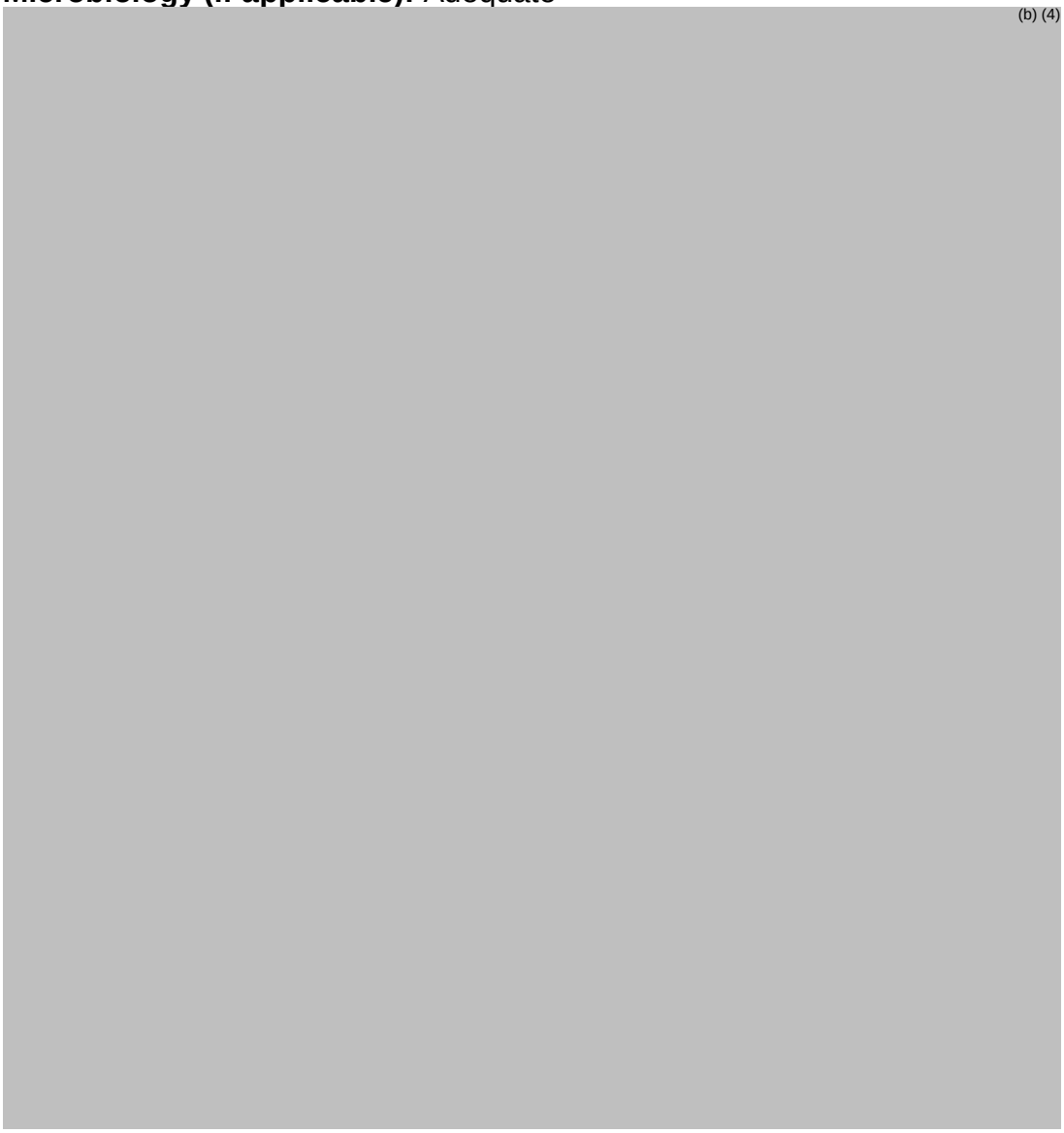
defined and adequately controlled. Some minor deficiencies were resolved via IR process.
The drug substance manufacturing facility has experience manufacturing the API with chemical synthesis process and has acceptable GMP compliance, and the recent GMP inspection was conducted on May 2016. The drug product manufacturing facility was last inspected for SVL in 2/6/2018. There are no current compliance issues with this firm and the facility is approvable based on district recommendation.

Biopharmaceutics: Choose an item.

N/A

Microbiology (if applicable): Adequate

(b) (4)



The specifications provided meet regulatory expectations. (b) (4) .

The applicant confirms that the USP compendial methodology is suitable for use during routine commercial production for release testing.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach** (b) (4)	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/Site	H		Acceptable	see micro reviewer Wendy Tan's review
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/Site	M		Acceptable	see micro reviewer Wendy Tan's review
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L		Acceptable	
Uniformity of Dose – Fill/deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L		Acceptable	
Osmolality following reconstitution	Formulation Raw materials Process parameters Scale/equipment/ site	L		Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L		Acceptable	
Particulate Matter	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	M		Acceptable	

Leachable Extractables	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L	(b) (4)	Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L		Acceptable	

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	10 July 2019	
	V			Active		
	III			Active		
	III			Active		Section 3.2.P.1 List of products ANNEX A Attachment 481

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	102486	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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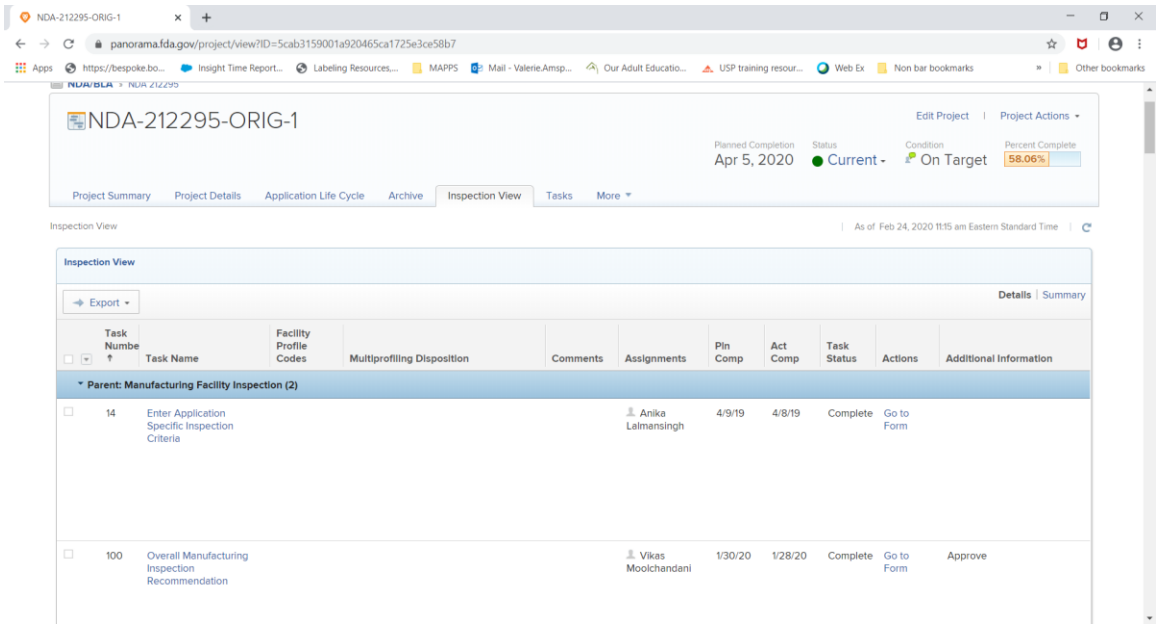

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Comparability Protocols

Assessment: *N/A*

Post-Approval Commitments

Assessment: *N/A*

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

This application is recommended for approval per labeling/labels perspective.

The quality-related items in the PI comply with regulatory requirements and are consistent with guidance recommendations, and CDER labeling policies.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yes	
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Yes	Single-patient-use

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Yes	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Yes	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Yes	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	N/A	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Yes	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Yes	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

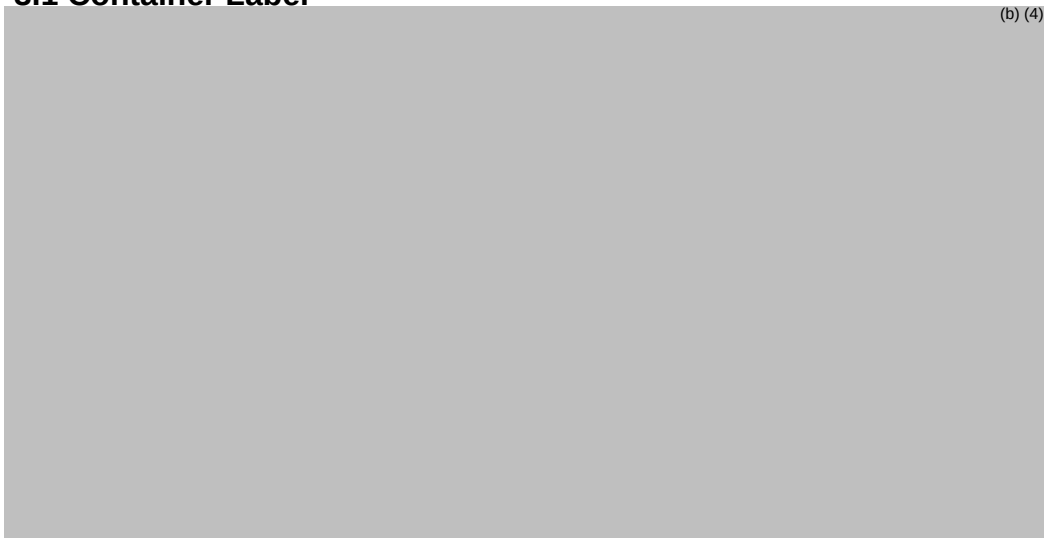
Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

This application is recommended for approval per labeling/labels perspective. The quality-related items in the PI comply with regulatory requirements and are consistent with guidance recommendations, and CDER labeling policies.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)



3.2 Carton Labeling

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes (container) / Yes (carton)	
Dosage strength	Yes (container) / Yes (carton)	
Route of administration	Yes (container) / Yes (carton)	Send IR (container)
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes (container) / Yes (carton)	Send IR (container)
Net contents (e.g. tablet count)	Yes (container) / Yes (carton)	
"Rx only" displayed on the principal display	Yes (container) / Yes (carton)	
NDC number	Yes (container) / Yes (carton)	
Lot number and expiration date	Yes (container) / Yes (carton)	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes (container) / Yes (carton)	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Yes (container) / N/A (carton)	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes (container) / Yes (carton)	

Item	Information Provided in the NDA	Assessor's Comments about Container/Carton Labeling
Name of manufacturer/distributor	Yes (container) / Yes (carton)	
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate.

This application is recommended for approval per labeling/labels perspective. The quality-related items in the PI comply with regulatory requirements and are consistent with guidance recommendations, and CDER labeling policies.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Valerie Amspacher

Digitally signed by Valerie Amspacher
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Julia Pinto

Digitally signed by Julia Pinto
Date: 2/27/2020 10:43:28AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: October 30, 2019

To: Valerie Amspacher, Drug Substance Reviewer
Julia Pinto, Supervisory Chemist
Anika Lalmansingh, RBPM

Through: Jason Rodriguez, Ph.D., Lab Chief, Branch I, CDER/OPQ/OTR/DPA

From: Dongping Dai, Chemist, Ph. D., OGROP/ORA/ORS/OMPTSLO
Phyllis Wilson, Supervisory Chemist, Ph. D., OGROP/ORA/ORS/OMPTSLO
Bruce Harris, Chemist, Ph. D., OGROP/ORA/ORS/OMPTSLO
Cynthia Sommers, MVP Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 212295: Remimazolam 20 mg, lyophilized powder for intravenous use

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Vial Content and Degradation Products
   Method: 3.2.P.5.2 Analytical Procedures [Remimazolam for Injection, Patheon Monza] Remimazolam for Injection.
2. Achiral Assay/Related Substances by HPLC.
   Method: 3.2.S.4.2 Analytical Procedures Remimazolam (Cambrex, Karlskoga) Document: 001473 Version: 1, Page 6.
3. Chiral Purity by HPLC
   Method: 3.2.S.4.2 Analytical Procedures Remimazolam (Cambrex, Karlskoga) Document: 001473 Version: 1, Page 14

Original analyst worksheets can be viewed using this ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f883a6ea8a

Summary of Analysis

Drug Substance (ACHIRAL)

Method Reference: ACHIRAL ASSAY/RELATED SUBSTANCES BY HPLC
3.2.S.4.2 Analytical Procedures Remimazolam (Cambrex, Karlskoga)
Document: 001473 Version: 1,

Identification: PASS

The sample peak retention time ((b) (4) min) matches that of the corresponding peak ((b) (4) min) in the standard solution.

Assay: PASS
Specification: (b) (4) % Remimazolam Besylate (on the anhydrous and solvent free basis)

Sample Preparation 1: (b) (4) %
Sample Preparation 2: %
Average Assay: (b) (4) %

Related substances by HPLC: PASS

Peak ID	RT Avg.2 prep	RRT Avg.2 prep	% Related Substance			RRF	Specification
			Prep. 1	Prep. 2	Avg. 2 Prep.		
(b) (4)							

Drug Substance (CHIRAL PURITY BY HPLC)

Method Reference: CHIRAL PURITY BY HPLC
3.2.S.4.2 Analytical Procedures Remimazolam (Cambrex, Karlskoga)
Document: 001473 Version: 1

CNC (b) (4) **PASS**
Sample Prep. 1: (b) (4) %
Sample Prep. 2: (b) (4) %
Average 2 Prep.: (b) (4) % (Limit: NMT (b) (4) %)

Drug Product: Remimazolam for Injection (20 mg)

Vial Content and Degradation Products:
Method Reference: 3.2.P.5.2 Analytical Procedures [Remimazolam for Injection, Patheon Monza] Remimazolam for Injection

Identification: PASS
Peak Retention Time: The sample peak retention time (15.3 min) matches that of the corresponding peak (15.0 min) in the standard solution.

Assay: PASS
Specification: 94-105.0%
(b) (4) mg/vial (Theoretical mg remimazolam /vial)
Assay Preparation 1: (b) (4) mg/vial
Assay Preparation 2: mg/vial
Average Assay: **mg/vial**

%Assay: 98.0%

Degradation Product: PASS
Specification (b) (4): Not more than (b) (4) % w/w

Peak ID	RT	RRT	%	RRF	Comments
(b) (4)					

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Remimazolam Besylate, lyophilized powder
NDA Number	212295
Assessment Cycle Number	1
Drug Product Name/ Strength	BYFAVO™ Remimazolam for Injection, 20 mg lyophilized powder for reconstitution (2.5 mg/mL, total 8 mL)
Route of Administration	Intravenous injection
Applicant Name	Cosmo Technologies, Ltd, Riverside II, Sir John Rogerson's Quay, Dublin 2, Bublin D02KV60, Ireland
Therapeutic Classification/ OND Division	Benzodiazepine indicated for induction and maintenance of procedural sedation
Manufacturing Site	Patheon Italia S.p.A., Viale G.B. Stucchi 110, Monza, MB 20900, Italy
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: *This Application is recommended for* ***Approval*** *based on sterility assurance. There are currently no deficiencies identified based on the information provided.*

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SN0000	04/05/2019
SN0008	05/28/2019
SN0010	07/09/2019
SN0014	08/15/2019
SN0017	09/16/2019
SN0019	09/30/2019
SN0037	01/28/2020

Highlight Key Issues from Last Cycle and Their Resolution: None. This is a 1st cycle review.

Remarks: This application is classified as Type 1 NME and Type 4 New Combination

Concise Description of Outstanding Issues: None

Supporting Documents:

- Type V DMF (b) (4) owned by (b) (4)., for their bacterial endotoxins reduction validation of the proposed (b) (4)
- Microbiology review (b) (4) mic8.doc dated 11/16/2015
- Microbiology review (b) (4).docx dated 04/11/2018
- Microbiology review (b) (4).docx dated 03/12/2019

S DRUG SUBSTANCE

Assessment: *N/A*

Drug substance is added to the excipients in (b) (4) of the drug product. Therefore, sterility assurance review will not be performed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** a white to off-white lyophilized powder filled in single-use clear glass vials. 20 mg.

- **Drug product composition** – see Table below:

Ingredient	Function	Content (vial)
Remimazolam besylate, in-house	API	(b) (4) mg
Lactose monohydrate, USP	Bulking agent/stabilizer	mg
Dextran 40, USP	(b) (4)	82. (b) (4) mg
(b) (4) USP		(b) (4)
HCl/NaOH, USP	pH adjustment	

- **Description of container closure system –**

Configuration	Component	Description	Manufacturer
20 mg lyophilized powder (8 mL of 2.5 mg/mL)	Vial	12 mL (b) (4) 20 mm clear glass vials	(b) (4)
	stopper	20 mm (b) (4) .	
	Seal	20 mm Aluminum seal with pp flip-off cap	

Validation Batches: (b) (4) L (b) (4) vials for each of 3 batches
Proposed Commercial Batch Size: (b) (4) L, (b) (4) vials

Vials are 100% inspected by the (b) (4) during the manufacturing of the validation batches.

Assessment: ***Adequate***

Drug product descriptions and container closure system is acceptable based on the information provided.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

[redacted]

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(b) (4)

Assessment: *Adequate*

The revised CCIT data is acceptable to resolve the deficiency.

Antimicrobial Effectiveness Testing

The subject drug product is a single-use vial containing no preservatives. Antimicrobial effectiveness test is not required.

Assessment: *Adequate*

The drug product unit vial is labeled for single-patient use containing no preservatives. Therefore, no AET is required.

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

Patheon Italia S.p.A, located at Viale G.B. Stucchi 110, 20900 Monza (MB), Italy, is responsible for manufacturing (b) (4) of the drug product (b) (4) .

Assessment: *Adequate*

The manufacturing site is identified with the DUNS and FEI provided in the submission.

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

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(b) (4)

Assessment: *Adequate*

The applicant confirms that the USP compendial methodology is suitable for use during routine commercial production for release testing.

P.7 CONTAINER CLOSURE

Assessment: *Please refer to P.1*

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

Proposed Expiry: 36 months

Assessment: *Adequate*

The applicant has provided stability data for up to 36M storage at 20º-25ºC long-term storage condition. The results met the expected release specifications for microbiological tests.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	NMT (b) (4) EU/vial
Sterility	USP <71>	Meets USP <71>

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

Stability storage conditions: 25° ± 2°C/60% ± 5%RH

Test	Time (Months)				
	0	12	24	36	48
Bacterial Endotoxins	X	X	X	X	X
Sterility	X	X	X	X	X

Post Approval Stability Commitment

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

Assessment: *Adequate*

The stability testing program committed by the Applicant is acceptable.

P.8.3 STABILITY DATA

Stability data are provided for vials placed in the upright and inverted position.

25°C/ 60% ± 5% RH
BET - < 16 EU/vial
Sterility – Meets USP <71>
Tested at initial, 12M, 24M, and 36M

40°C/75% RH:
BET - < 16 EU/vial
Sterility – Meets USP <71>
Tested at initial and 6M

Assessment: *Adequate*

The stability data provided met the release specifications and is acceptable.

R REGIONAL INFORMATION

Executed Batch Records

Executed lot #(s): Registration Batches 20001, 20002, and 20003; validation batches 00001, 00002, and 00003

The batch records confirm that the executed batches were produced using validated sterilization/depyrogenation and (b) (4) manufacturing processes. The records indicated that (b) (4)

Assessment: *Adequate*

Information provided for the validation batches is acceptable.

Comparability Protocols

Assessment: *N/A*

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

2.A. Prescribing Information

- Post-dilution/constitution hold time

PACKAGE INSERT

(1.14.1.3 package insert, 5/28/2019 submission)

Storage temperature: 20°- 25°C (68° to 77°F)
Route of administration: intravenous injection
Container: Single-use vial

Reconstituted/Further Diluted Drug Product (05/28/2019 submission)
The package insert states that "*The product must be prepared immediately before use* (b) (4)

- *Reconstituted TRADENAME* (b) (4) *up to 8 hours under controlled room temperature at 20ºC to 25ºC (68ºF to 77ºF)*"

No adventitious microbial risks assessment is provided in the submission. The following IR was communicated to the Applicant during the filing review:

(b) (4)

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Assessment: *Adequate*

The microbial stability data supports that storage instruction described in the drug product package insert for extended storage of the reconstituted product for 8 hours at (b) (4) 20ºC to 25ºC.

Post-Approval Commitments

Assessment: *N/A*

U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY LIST OF DEFICIENCIES

Based on the information provided, there are currently no deficiencies identified.

Primary Microbiology Assessor Name and Date:
Wendy Tan, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMA I/B2
February 03, 2020

Secondary Assessor Name and Date:
Bryan Riley, Ph.D.
Branch Chief
CDER/OPQ/OPMA/DMA I/B2 & 5
February 03, 2020

Wendy Tan

Digitally signed by Wendy Tan
Date: 2/03/2020 12:56:21PM
GUID: 52937cdc0000cf21a0a712ca83253bcb

Bryan Riley

Digitally signed by Bryan Riley
Date: 2/03/2020 12:08:34PM
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/s/

VALERIE R AMSPACHER
02/27/2020 02:31:22 PM