CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212839Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approve

NDA 212839

Review # 1

Drug Name/Dosage Form	Xcopri™ (cenobamate) tablets
Strength	12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg and 200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	SK Life Science, Inc
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	Charles Jewell	Su Tran
Drug Product/Labeling	Andrei Ponta	Wendy Wilson-Lee
Manufacturing	Sydney Choi	Nallaperumal Chidambaram
Biopharmaceutics	Akm Khairuzzaman	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia A. Woody	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

Amendments Reviewed

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-001, Original NDA	11/21/2018	All
SD-005, Response to IR	1/31/2019	Manufacturing
SD-009, Response to IR	2/22/2019	Drug Substance
SD-010, Labeling/Package Insert	3/21/2019	Product/Labeling
SD-015, Labeling/Container-Carton	5/9/2019	Product/Labeling
SD-016, Response to IR	6/21/2019	Product, Manufacturing
SD-017, Response to IR	7/8/2019	Product

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III		(b) (4)	N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	

[1] Adequate information in application or DMF previously reviewed with no later changes.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	(b) (4)
INDs	(b) (4)	

2. CONSULTS: N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 212839 for Xcopri (cenobamate) tablets. From a quality perspective, the application provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Cenobamate (YKP3089), a new molecular entity, is a novel antiepileptic drug developed by SK Life Science (SK) for treatment of partial onset seizures. The mechanism of action for cenobamate is not fully characterized, however, it has been shown to reduce repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. It is also a positive allosteric modulator of six subtypes of the γ-aminobutyric acid ion channel. The applicant proposes marketing cenobamate as immediate release tablets in six strengths, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg and 200 mg, with the lowest three strengths intended primarily for dose titration.

Proposed Indication(s) including Intended Patient Population	Treatment of partial onset seizures in adult patients.
Duration of Treatment	Chronic
Maximum Daily Dose	400 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

The bulk active pharmaceutical ingredient (API), cenobamate, is a well characterized, neutral, small molecule that is slightly soluble in aqueous media across the pH range (b) (4) (b) (4) The bulk drug substance is manufacture (b) (4) (b) (4)

The applicant has adequately characterized the chemical structure and physicochemical properties of the drug substance using conventional spectroscopic methods, X-ray

crystallography and physicochemical tests. Appropriate controls are used during manufacture and release to ensure critical quality attributes, including identity, strength, purity, and physical characteristics suitable for manufacture of the drug product. Acceptance criteria for related substances are consistent with ICH identification and qualification thresholds. Based on the applicant's risk assessment for elemental impurities (per ICH Q3D), no controls for elemental impurities are proposed for the drug substance. Potential mutagenic impurities (per ICH M7) are adequately controlled during manufacture and omission of testing for specified mutagenic impurities at release is justified. All analytical procedures are adequately described and validated.

Stability data provided in the application support the requested (b) (4)-*month retest period* for drug substance stored a (b) (4)

Drug Product

Xcopri tablets are immediate-release tablets that contain 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg or 200 mg cenobamate (b) (4)
(b) (4)

The formulations of the to-be-marketed film coated tablets are the same as the Phase 3 clinical-tablets, except for coating color changes. The provided dissolution profile comparison data fully support the bridging between Phase 3 and to-be-marketed tablets. Early stage (Phase 1 and 2) formulation bridging was accomplished via human BE studies and similar dissolution profiles.

Xcopri tablet (b) (4) will be packaged in (b) (4)-count high-density polyethylene (HDPE) bottles. (b) (4)
(b) (4) All tablet strengths will be packaged i (b) (4) 14-count (b) (4) blister configurations.

The manufacturing process for Xcopri tablets includes (b) (4)
(b) (4). The manufacturing process and process controls are deemed acceptable.

The drug product specification includes tests for all critical quality attributes, including appearance, identity, assay, related substances, content, dissolution (b) (4) chiral purity, and microbial limits. Based on the applicant's risk assessment, testing for elemental impurities is not needed (per ICH Q3D). Analytical procedures are adequately described and validated. The specification, as proposed by the applicant, is deemed acceptable on review. No revisions were requested during the NDA review.

Based on the stability data provided in the submission, the *expiration dating periods* listed below are granted for product stored under controlled room temperature conditions. Shelf-life may be extended post-approval as additional long-term data are obtained.

- 12.5 mg and 25 mg tablets: 30 months
- 50 mg and 100 mg tablets: 36 months
- 150 mg and 200 mg tablets: 18 months

Facilities

All facilities that will be involved in commercial manufacture and testing of cenobamate and Xcopri (cenobamate) tablets are currently acceptable.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31(b). Approval of the application is expected to increase use of the active moiety; however, the expected environmental introduction concentration (EIC) is less than 1 part per billion and there are no extraordinary circumstances. The claim is granted.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment

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, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale • Equipment • Site	L	Use of compatible excipients, control of manufacturing parameters, and packaging. Registration and supportive stability studies	Adequate	
Physical stability, solid state		L	(b) (4) (b) (4)	Adequate	
Content uniformity		L	Applicant will perform in-process tests (b) (4) (b) (4)	Adequate	
Microbial limits		L	Applicant tests at release and on stability.	Adequate	
Dissolution		L	Active ingredient is highly soluble across physiological pH range and appropriate test method and acceptance criteria are established.	Adequate	

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Heimann

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	212839
Drug Product Name/ Strength	Cenobamate (YKP3089) Tablets/12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg and 200 mg
Route of Administration	Oral
Applicant Name	(b) (4)
Therapeutic Classification/ OND Division	Division of Neurology Products
Proposed Indication	Partial Onset-Seizures
Primary Reviewer	Akm Khairuzzaman, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: Adequate

Assessment Summary:

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting **1)** the proposed dissolution method and acceptance criteria, and **2)** bridging throughout product development. Key Biopharmaceutics review findings based on the review of the provided information/data are summarized as follows:

1) ***Dissolution Method and Acceptance Criteria:*** The Applicant's proposed dissolution method [USP apparatus II (Paddle) at 75 rpm; 500 mL (12.5 mg) & 900 ml (50, 100, 150 & 200 mg) of 0.01N HCl at 37°C] and acceptance criterion of Q (b) (4)% at 30 min are **acceptable** for release and on stability.
2) ***Bridging of Formulations:*** The formulation of the Phase III-film coated tablets is the same as the to-be-marketed tablets, except for the coating color chang (b) (4) (b) (4). The provided dissolution profile comparison data fully support the bridging between Phase III and to-be-marketed drug products. Early stage (Phase I and II) formulation bridging was accomplished via human BE studies and similar dissolution profiles. There is no manufacturing site change between the clinical Phase III and commercial batches.
3) ***Risk Assessment:*** The following table summarizes the initial and final risk assessment.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 0001	Comments
Dissolution	Medium to low	Potential BCS class 1 drug. Risk is depending on (b) (4) (b) (4) dissolution method development and associated PK studies (e.g. bioavailability studies during formulation screening)	Low	Please see overall biopharmaceutics risk assessment under Appendix 1.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001	11/21/2018

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Applicant submitted report (# 15SKBIP1R3GLPS303)[1] on in vitro permeability and solubility study according to FDA's Biopharmaceutics Classification System (BCS) guideline. The following solubility and permeability data were provided in the application.

Tab 1. pH solubility data

pH	Buffer	Measured Concentration (nM)	Measured Concentration (mg/mL)	Mean (mg/mL)	SD (mg/mL)	CV (%)	Volume to Dissolve HDS (mL)[a]
1.0	HCl	7570000	2.03	1.93	0.0837	4.34	20.7
		7350000	1.97				
		6990000	1.87				
		6900000	1.85				
3.0	Acid phthalate	7990000	2.14	2.04	0.0905	4.43	19.6
		7830000	2.10				
		7270000	1.95				
		7420000	1.99				
5.0	Neutralized phthalate	7930000	2.12	2.08	0.0476	2.29	19.3
		7510000	2.01				
		7760000	2.08				
		7820000	2.09				
6.8	Phosphate	6460000	1.73	1.88	0.131	6.98	21.3
		6730000	1.80				
		7430000	1.99				
		7410000	1.98				

Tab 2. Unidirectional permeability data (n=4)

Nominal YKP3089 Dosing Concentration		14.9 µM	149 µM	2.99 mM
YKP3089	P_{app} (10^{-6} cm/s)[a]	43.3 ± 9.74	42.6 ± 17.1[b]	48.2 ± 8.04
	Recovery (%)[a]	99.7 ± 5.13	83.6 ± 4.43	91.1 ± 5.97
Minoxidil (10 µM)	P_{app} (10^{-6} cm/s)	3.64 ± 0.343	3.08 ± 0.657	5.56 ± 1.60
	Recovery (%)	103 ± 3.36	93.2 ± 2.50	97.4 ± 3.01
Atenolol (100 µM)	P_{app} (10^{-6} cm/s)	0.123 ± 0.0330	0.185 ± 0.0319[c]	0.275 ± 0.0757
	Recovery (%)	101 ± 1.04	90.8 ± 2.18[c]	92.8 ± 1.13

Tab 3. Bidirectional permeability data (n=4)

[1] \\cdsesub1\evsprod\NDA212839\0001\m4\42-stud-rep\422-pk\4227-other-pk-stud\15skbip1r3clps303

Parameter	Direction	YKP3089 Dosing Concentration		
		14.9 µM	149 µM	2.99 mM
P_{app} (10^{-6} cm/s)	A-to-B	28.2 ± 14.7[a]	34.3 ± 4.08[b]	42.1 ± 14.6
Recovery (%)		97.6 ± 1.40	84.5 ± 2.21	86.8 ± 3.04
P_{app} (10^{-6} cm/s)	B-to-A	43.1 ± 5.06	36.9 ± 7.28[b]	40.9 ± 2.99
Recovery (%)		105 ± 4.41	96.8 ± 3.48	101 ± 3.92
Efflux Ratio*		1.53	1.08	0.972

Since the permeability of the test article, YKP3089, was higher than that of minoxidil, and minoxidil is at least 90% absorbed in humans, it can be inferred that YKP3089 should have greater than 90% absorption in humans.

In Vivo Mass balance study: In a mass balance study in humans (Study AA41857), after administration of a single oral dose of [14C]-cenobamate 400 mg, reported approximately 88% of the administered radioactive dose was recovered in urine primarily as metabolites. Defer to Office of Clinical Pharmacology (OCP) for acceptability of the study results.

Assessment: Acceptable.

No formal BCS designation claim has been submitted to the FDA (b) (4) (b) (4) (b) (4) This is a SUPAC Level II formulation differences and therefore the FDA suggested (Ref. pre-NDA meeting minutes 04 Apr 2018, Q # 7)[2] that a BCS class I based bridging approach may be suitable to bridge such formulation differences. In response to FDA's recommendation, the Applicant opted to pursue the bridging through in vivo human BE study. In addition to that, the Applicant has also submitted a BCS designation document. Since the applicant has conducted a BE study, the BCS based biowaiver is therefore not relevant and there is no biowaiver request based on BCS classification system. However, based on the solubility data, permeability data and the mass balance study, it appears the drug substance belongs to BCS class I category. It is to note that the Applicant did not ask for any regulatory flexibility in their application based on the BCS class.

Solubility: Based on the pH solubility data provided (Table 1 & 2), the drug substance is considered as a highly soluble drug, considering the highest strength and maximum dose being 200 mg and 400 mg, QD, respectively. Cenobamate drug substance has a solubility of 1.7 mg/mL over physiologic pH range (0.1 N HCl to pH 8 sodium phosphate buffer). The drug substance is neutral and non-ionizable for the pH range studied.

Permeability: In vitro permeability data and radiolabeled human mass balance data suggest high permeability of the drug substance.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The dissolution method and dissolution acceptance criteria proposed by the Applicant for the proposed drug product are presented below.

[2] \\cdsesub1\evsprod\NDA212839\0001\m1\us\16-meet

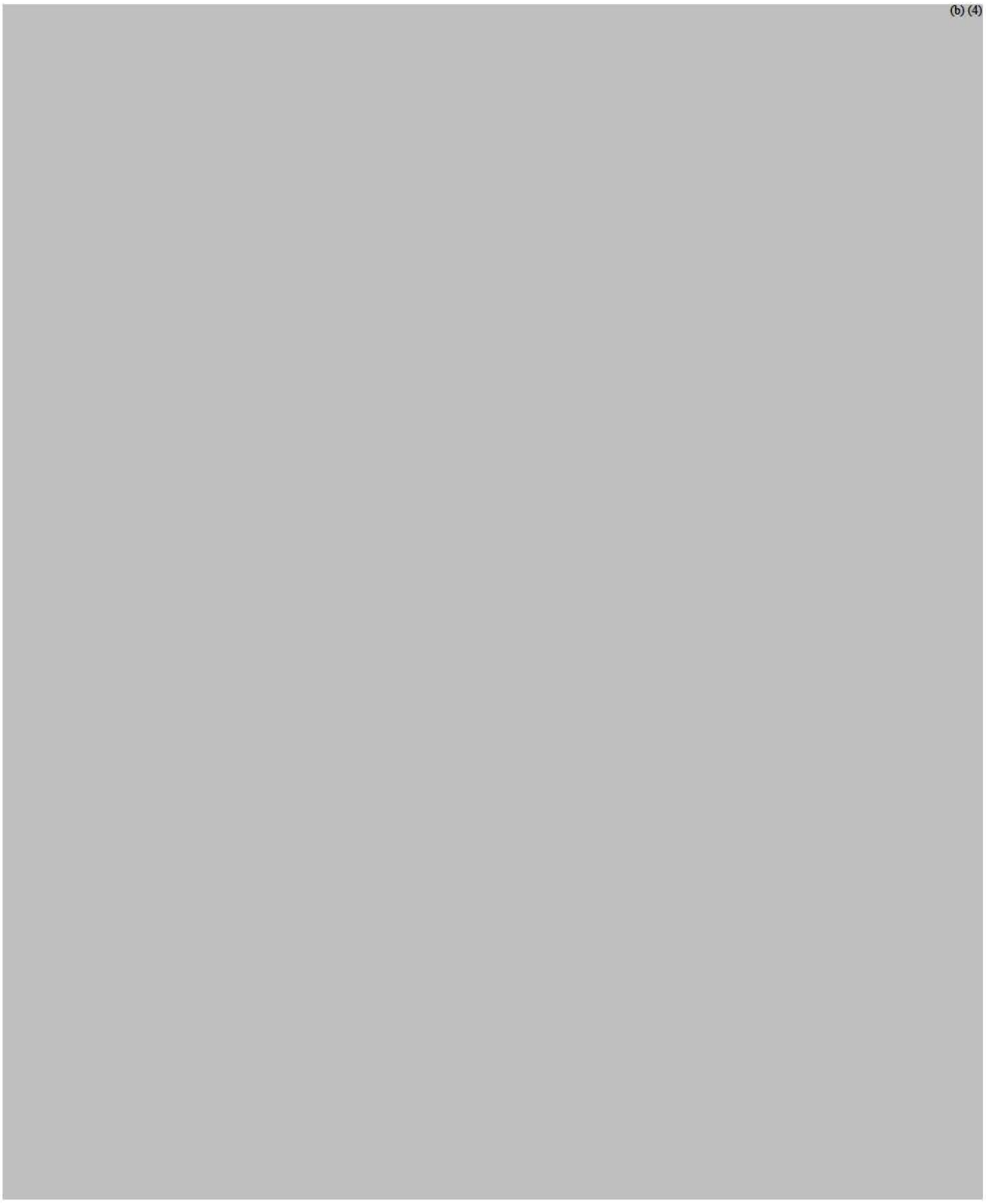
USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Analytical Method	Proposed Acceptance Criteria
II (Paddle)	75	0.01N HCl	500/37 for the 12.5 mg strength 900/37 for the 50 mg, 100 mg, 150 mg & 200 mg strengths	HPLC	NL (b) (4)% Dissolved (Q (b) (4)) in 30 minutes

Dissolution method development: Dissolution method development (module # 2.1.4.1) was provided in the Application and can be accessed via the link[3]. The drug product dissolution testing was carried ou (b) (4)

(b) (4)

[redacted]

[3] \\cdsesub1\evsprod\NDA212839\0001\m3\32-body-data\32p-drug-prod\cenobamate\32p2-pharm-dev



Assessment: *Adequate*

Dissolution method was appropriately developed considering all the parameters such as medium composition, volume, pH, spee (b) (4)

(b) (4)

(b) (4) Based on risk to benefit analysis, this Reviewer accepts the proposed method for routine quality control at batch release and on stability.

The dissolution limit proposed is acceptable based on statistical analysis on the historical data of clinical and registration batches and stability batch data.

B.3 BRIDGING OF FORMULATIONS

Table 6. Drug Product Comparison Between Clinical Trial Material and Proposed Commercial Use

Drug product description for clinical trial material[c]	Drug product description for proposed commercial use[c]
Capsules (All strengths are white (b) (4) capsules) 5 mg, 25 mg, 50 mg and 100 mg	**No capsules proposed for commercial**
Tablets 1. 12.5 mg (b) (4) (b) (4) 2. 25 mg (b) (4) (b) (4) 3. 50 mg (b) (4) (b) (4) 4. 100 mg (b) (4) (b) (4) 5. 150 mg (b) (4) (b) (4) 6. 200 mg (b) (4) (b) (4)	**Tablets** 1. 12.5 mg (b) (4) (b) (4) 2. 25 mg (b) (4) (b) (4) 3. 50 mg (b) (4) (b) (4) 4. 100 mg (b) (4) (b) (4) 5. 150 mg (b) (4) (b) (4) 6. 200 mg (b) (4) (b) (4)

[a] Drug product image not proposed in commercial but used for clinical trials

[b] Drug product image proposed in commercial but not used for clinical trials

[c] The shape of all the strengths used in clinical studies is the same as proposed commercial and therefore not included in the table; all tablets are round except the 200 mg tablets, which are oval.

The significance of the comparative dissolution of different formulations/product images (above table) was discussed with FDA via Type C written responses on 16 March 2018. According to FDA's advice, the Applicant has submitted the F2 comparison as follows:

Table 6. F2 similarity data:

ID No.	Batch Number	Dosage Strength and Form	Dissolution Testing Conditions[1]	F2 Value	Reference Section
1	KCTD	100 mg tablet	0.01N HCl[2]	52	Section 2.1.4.2.1
	HWCF	100 mg capsule			
2	KCTC	50 mg tablet	0.01N HCl[2]	61	
	HWCD	50 mg capsule			
3	SBKC	25 mg tablet, (b) (4) mg core weight)	(b) (4)	--[3]	Section 2.1.4.2.2
	WDMG	25 mg tablet, (b) (4) mg core weight)			
4	SBKC	25 mg tablet, (b) (4) mg core weight)		--[3]	
	WDMG	25 mg tablet, (b) (4) mg core weight)			
5	SBKC	25 mg tablet, (b) (4) mg core weight)		--[3]	
	WDMG	25 mg tablet, (b) (4) mg core weight)			
6	VDNN	50 mg (b) tablet		--[3]	Section 2.1.4.2.3
	ZTPB	50 mg yellow tablet			
7	VDNN	50 mg (b) tablet		--[3]	
	ZTPB	50 mg yellow tablet			
8	VDNN	50 mg (b) tablet		--[3]	
	ZTPB	50 mg yellow tablet			
9	XHCV	100 mg brown (1 tablet)	0.01 N HCl	--[3]	Section 2.1.4.2.4
	YWWZ	200 mg light orange (1 tablet)			
	XHCV	100 mg brown, (2 tablets)			
10	TVNF	50 mg (b) tablet	0.01N HCl[4]	C of A Comparison	Section 2.1.4.2.5
	VYKN	100 mg brown tablet			

[1] Not needed as individual dissolution is (b) (4)
[2] Not needed as mean dissolution is (b) (4)
[3] Dissolution conditions are 900 mL and 75 rpm
[4] n=6
[5] n=12
[6] n=24 (USP <711> stage 3 testing)

Since both the 50 mg and 100 mg tablets used in clinical studies had the same diameter, tablet weight and coating colo (b) (4) a change was made to better differentiate the 50 mg tablets from the 100 mg tablets. Th (b) (4) coating of 50 mg tablets were changed t (b) (4) yellow coating. As per the recommendation made by FDA via Type C written responses (March 16, 2018), comparative dissolution study was performed in multimedia. No significant difference was observed (Ref. 3.2.P.2 Pharmaceutical Development, pages 26 through 28).

Assessment: *Adequate*

Bridging of Phase 1 Clinical Tablets to Phase 1 Clinical Capsule: Cenobamate was originally developed as an oral capsule formulation; at the end of Phase 1 study the formulation was changed to a tablet dosage form. The bridging was established through a relative bioavailability study (YKP3089C019[4]) and comparative dissolution profiles showing f2 >50. Results were acceptable at 90% confidence interval.

Bridging of lower strengths (12.5 mg, 25 mg, 50 mg) to higher strengths (100 mg, 150 mg, 200 mg), a Level II SUPAC formulation change (b) (4) (b) (4) (b) (4) Therefore, the bridging study (YKP3089C032[5])

[4] \\cdsesub1\evsprod\NDA212839\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\ykp3089c019

[5] \\cdsesub1\evsprod\NDA212839\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\ykp3089c032

was performed between the 50 mg or 200 mg tablet with the 100 mg table (b) (4) (b) (4)

through a relative BE study. Results were acceptable at 90% confidence interval. The bridging is ***Adequate.***

Bridging of Clinical to to-be-marketed Drug Product: The formulation of the Phase III-film coated tablets is the same as the to-be-marketed tablets, except for the coating color. The film coating componen (b) (4) used in the Phase III tablets was changed t (b) (4) (b) (4) for the to-be-marketed tablets. The provided dissolution profile comparison data fully support the bridging between Phase III and to-be-marketed drug products. The bridging is ***Acceptable.***

Bridging of Manufacturing Sites for Clinical Supplies and Commercial Drug Product: There is no change in the manufacturing sit (b) (4) . ***Acceptable.***

B. 13 BIOWAIVER REQUEST

Assessment: None

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: None

Post-Approval Commitments

Assessment: None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

APPENDIX 1

OVERALL BIOPHARMACEUTICS RISK ASSESSMENT: Low

Failure mode/Risk Factor		Likelihood to impact Dissolution	Reviewer's Rational
Raw Material Attributes	API PSD & polymorphism	Low	A potential BCS class 1 drug. Highly soluble and highly absorbable drug, supported by detailed pH solubility data and in vitro and in vivo permeability data. Therefore, from biopharmaceutics perspective PSD variation is less likely to impact dissolution (unless the PSD is extremely different). Additionally (b) (4) API PSD control is in place with established test and limit in specification. Additionally, the dissolution method showed discriminating capability with respect to API particle size variation.
	Excipient variability	Low	Effect of formulation variability (tablet vs capsules) showed no difference in bioavailability (Study # YKP3089C019). Therefore, risk of excipient variability is very low. Additionally, variability of excipient within the tablet dosage form from (e.g (b) (4) (b) (4)) did not have any impact on dissolution.
Manufacturing process parameters from various unit operation	(b) (4)	Low	Does not have any impact on dissolution.
		Low	(b) (4)
		Low	No impac (b) (4) on dissolution within the range established.

[6] \\cdsesub1\evsprod\NDA212839\0001\m3\32-body-data\32p-drug-prod\cenobamate\32p2-pharm-dev

Analytical method sensitivity /discriminating capability	Likelihood to release any defective batch by the developed dissolution method is **very low**	Appropriate statistical sampling plan from every batch is in place (b) (4) (b) (4) (b) (4)

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

(b) (4)

[redacted]

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	XCORPI (cenobamate tablets), for oral use
Dosage form, route of administration	Tablets, oral
Controlled drug substance symbol	Pending
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg

Is the information accurate? ☒ Yes ☐ No

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

TRADENAME tablets may be taken any time with or without food (b) (4) [redacted] (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation	None

Is the information accurate? ☒ Yes ☐ No

3. ***Section 3 Dosage Forms and Strengths***

3 DOSAGE FORMS AND STRENGTHS

TRADENAME tablets are available in the following strengths, shapes, colors and tablet markings (Table 1).

Table 1: TRADENAME Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
12.5 mg	Uncoated round white to off-white tablets	SK on one side and 12 on the other side
25 mg	Film coated round brown tablets	SK on one side and 25 on the other side
50 mg	Film coated round yellow tablets	SK on one side and 50 on the other side
100 mg	Film coated round brown tablets	SK on one side and 100 on the other side
150 mg	Film coated round light orange tablets	SK on one side and 150 on the other side
200 mg	Film coated modified oval light orange tablets	SK on one side and 200 on the other side

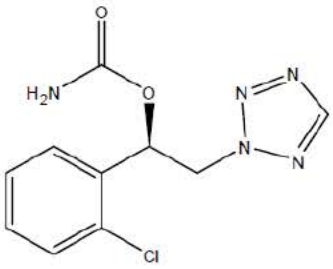
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Active moiety expression of strength with equivalence statement	Cenobamate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tablets debossed with "SK" on one side and the strength (e.g. 12, 25) on the other side. Each strength has a different color: the 12.5 mg strength is white to off-white; 25 mg strength is brown; 50 mg strength is yellow; 100 mg strength is brown; 150 mg strength is light orange; and the 200 mg strength is light orange. All tablets are round with the exception of the 200 mg strength which is oval

Is the information accurate? ☒ Yes ☐ No

4. ***Section 11 Description***

11 DESCRIPTION

The chemical name of TRADENAME (cenobamate) is [(1*R*)-1-(2-Chlorophenyl)-2-(tetrazol-2-yl) ethyl] carbamate. Its molecular formula is $C_{10}H_{10}ClN_5O_2$ and its molecular weight is 267.67 g/mol. The chemical structure is:



TRADENAME is a white to off-white crystalline powder. It is very soluble in aqueous solutions (water 1.7 mg/mL) and has higher solubility in organic solvents like ethanol (209.4 mg/mL).

Tablets

TRADENAME tablets are for oral administration and contain the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate and film coating agents specified below:

12.5 mg tablets: Not Applicable, since 12.5 mg tablets are uncoated.

25 mg and 100 mg tablets: FD&C Blue# 2/indigo carmine aluminum lake, iron oxide red, iron oxide yellow, polyethylene glycol 3350, polyvinyl alcohol-part hydrolyzed, talc and titanium dioxide.

50 mg tablets: iron oxide yellow, polyethylene glycol 3350, polyvinyl alcohol-part hydrolyzed, talc and titanium dioxide.

150 mg and 200 mg tablets: iron oxide red, iron oxide yellow, polyethylene glycol 3350, polyvinyl alcohol-part hydrolyzed, talc and titanium dioxide.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	XCORPI (cenobamate tablets)
Dosage form and route of administration	Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Active moiety expression of strength with equivalence statement (if applicable)	Cenobamate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The drug product contains the following USP/NF excipients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate, . The tablets are coated with (b) (4) coatings that contain the following excipients: FD&C BLUE #2/Indigo Carmine Aluminum lake, iron oxide red, iron oxide yellow (b) (4) PEG, polyvinyl alcohol,

	talc, titanium dioxide.
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Not included Reviewer's Note: Applicant will be asked to remove statement about enteric coating
Chemical name, structural formula, molecular weight	$C_{10}H_{10}ClN_5O_2$ – 267.67 g/mol
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Soluble in ethanol

Is the information accurate? ☒ Yes ☐ No

5. *Section 16 How Supplied/Storage and Handling*

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

Dosage Strength/Quantity	Packaging	NDC
12.5 mg/14 count and 25 mg/14 count	Blister, Titration Pack	71699-201-28
50 mg/30 count	Bottle	71699-050-30
(b) (4)		
50 mg/14 count and 100 mg/14 count	Blister, Titration Pack	71699-202-28
(b) (4)		
50 mg/28 count and 200 mg/28 count	Blister, Maintenance Pack	71699-102-56
100 mg/30 count	Bottle	71699-100-30
(b) (4)		
150 mg/30 count	Bottle	71699-150-30
(b) (4)		
150 mg/14 count and 200 mg/14 count	Blister, Titration Pack	71699-203-28
(b) (4)		
150 mg/28 count and 200 mg/28 count	Blister, Maintenance Pack	71699-103-56
200 mg/30 count	Bottle	71699-200-30
(b) (4)		

16.2 Storage and Handling

Store TRADENAME tablets at 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F) (*See USP Controlled Room Temperature*). Keep out of reach of children.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Available units (e.g., bottles of 100 tablets)	Strength (mg) / Count / Packaging Configuration 50, 100, 150 and 200 / 30 / (b) (4) (b) (4) 12.5, 25, 50,100, 150 and 200 / (b) (4) 14
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablets debossed with "SK" on one side and the strength (e.g. 12, 25) on the other side. Each strength has a different color: the 12.5 mg strength is white to off-white; 25 mg strength is brown; 50 mg strength is yellow; 100 mg strength is brown; 150 mg strength is light orange; and the 200 mg strength is light orange. All tablets are round with the exception of the 200 mg strength which is oval
Special handling	Not Applicable
Storage conditions	USP controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	SK Life Science, Inc.

Reviewer's Assessment of Package Insert: ***Adequate***

Prescribing Information complies with all regulatory requirements from a CMC perspective.

However, some revisions have been identified and will be communicated to the Applicant as part of DNP labeling negotiations.

II. Labels:

1. *Bottle Labels*

(b) (4)

2. ***Blister Label***

(b) (4)

Item	Information provided in the bottle label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	XCORPI (cenobamate tablets)
Dosage strength	Complies
Net contents	Complies
"Rx only" displayed prominently on the main panel	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies
Lot number and expiration date (21 CFR 201.17)	Complies
Storage conditions	Complies
Bar code (21CFR 201.25)	Complies
Name of manufacturer/distributor	Complies
And others, if space is available	Not Applicable

Reviewer's Assessment of Labels: ***Adequate***

The container labels comply with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, net contents, strength, and the name (proprietary and established).

List of Suggested Edits Communicated to Applicant:

1. *Include the pharmacological class as part of the description section of the PI.*

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta, Ph.D. 1-Jul-2019

Andrei Ponta

Digitally signed by Andrei Ponta
Date: 7/03/2019 10:38:19AM
GUID: 53b58e0b00004a630e714ee170af4c26

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/03/2019 10:46:28AM
GUID: 50816dbc000085595ca3284bbca465a8