

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210833Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

**NDA 210833
Review # 1**

Drug Name/Dosage Form	Clobazam Oral Film
Strength	5 mg, 10 mg, 20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Aquestive Therapeutics (formerly MonoSol Rx, LLC)
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Original</i>	29-NOV-2017
<i>Amendment</i>	15-FEB-2018
<i>Amendment</i>	10-MAY-2018
<i>Amendment</i>	22-MAY-2018
<i>Amendment</i>	22-JUN-2018
<i>Amendment</i>	06-JUL-2018

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Gaetan Ladouceur	Charles Jewell	ONDP
Drug Product	Milton Sloan	Wendy Wilson-Lee	ONDP
Environmental			
Labeling	Peter Krommenhoek	Nallaperumal Chidambaram	OPF
Process			
Microbiology	Ephrem Hunde	Ruth Moore	OPF
Facility	Ho-pi Lin	Poonam Delvadia	ONDP
Biopharmaceutics	Dahlia Walters		OPRO
Regulatory Business Process Manager	Wendy Wilson-Lee		ONDP
Application Technical Lead			

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	Type II		(b) (4)	Adequate	30-OCT-2017	
	Type III		Not reviewed	-	Sufficient information provided in NDA	
	Type IV		Not reviewed	-	Sufficient information provided in NDA	
	Type IV		Not reviewed	-	Sufficient information provided in NDA	
	Type IV		Not reviewed	-	Sufficient information provided in NDA	
	Type IV		Not reviewed	-	Sufficient information provided in NDA	
	Type IV		Not reviewed	-	Sufficient information provided in NDA	
	Type IV		Not reviewed	-	Sufficient information provided in NDA	
	Type IV		Not reviewed	-	Sufficient information provided in NDA	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	129383	Clobazam Oral Soluble Film
NDA	202067	ONFI (listed drug)

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210833 for Clobazam Oral Film, 5, 10, and 20 mg.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	<i>Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years and older</i>
Duration of Treatment	<i>Chronic</i>
Maximum Daily Dose	<i>40 mg</i>
Alternative Methods of Administration	<i>None</i>

The Applicant is seeking approval of Clobazam Oral Film as an adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years and older. The oral film dosage form is an alternative dosage form to the RLD Clobazam Tablets (NDA 202067, approved October 2011). Clobazam is also approved as an oral suspension (NDA 203993, approved December 2012). FDA did not grant any regulatory designations (e.g. fast track, breakthrough, etc.) for this product. FDA reached agreement with the Applicant regarding the initial Pediatric Study Plan in October 2017.

OPQ provided advice regarding the drug product stability program and excipient qualification as part of a Type B Pre-IND WRO Meeting in March 2016. The drug product is a white, rectangular film for oral administration (b) (4)

(b) (4). The 5 mg, 10 mg, and 20 mg strength products are dose proportional and manufactured using a single (b) (4) formulation. During manufacturing, (b) (4)

(b) (4)

(b) (6). The Applicant contends that the oral film offers ease of administration compared to the currently approved products as it only requires placement for administration.

Key review issues included adequacy of the control strategy to ensure assay and content uniformity (b) (4) to determine product strength; evaluation of the robustness of the film at release and over the proposed shelf-life to ensure the proposed product is commercially viable; establishment of a suitable drug product expiration date; suitability of the in vitro release method to detect differences in product quality; and evaluation of product palatability to foster patient compliance.

B. Quality Assessment Overview

Clobazam is a white or almost white, crystalline powder with a slightly bitter taste; is slightly soluble in water and sparingly soluble in ethanol. The melting range of clobazam is from 182°C to 185°C. Clobazam is a member of the benzodiazepine pharmacological class of compounds and is a Schedule IV drug. Clobazam drug substance information is cross-referenced to DMF (b) (4). The Applicant provided sufficient information regarding the general characteristics of the drug substance. The drug substance specification includes all tests and acceptance criteria as listed in the Eur. Ph. Monograph along with a the USP Residual Solvents method and in-house methods for appearance and particle size. Drug substance batch analysis results for three batches confirm compliance with the specification.

Clobazam Oral Film is a white, rectangular film for oral administration (b) (4). (b) (4). The 5 mg, 10 mg, and 20 mg strength products are dose proportional and manufactured using a single (b) (4) formulation. Clobazam Oral Film is packaged in a (b) (4) pouch (b) (4). (b) (4). A quality target product profile was established to ensure the safety and performance of the product. The speed and quantity of absorption for the oral film match the pharmacokinetic profile of the RLD. The dosage form is not intended to be swallowed intact. (b) (4) and dissolves, releasing the active ingredient into the saliva for subsequent gastric absorption.

The excipients are compendial grade (USP/NF or Ph.Eur), generally recognized as safe (GRAS), or have been used in approved drug products. The levels of each excipient are less than the maximum reported amounts in the IIG or other approved oral film products. Maltitol (b) (4). (b) (4) The taste masking excipients are incorporated at appropriate levels to mask the slightly bitter taste of the clobazam.

The drug product specification is adequate to ensure quality for the dosage form. A risk assessment of the elemental impurities per ICH Q3D guidelines demonstrated that the elemental impurities that may be present in the drug product from all potential sources are lower than the permitted daily exposure. Clobazam degrades under acidic and basic forced degradation conditions; however, analysis of samples stored at room temperature conditions for twelve months showed no trend in assay and individual and total impurities remained below the specification limits. No unknown impurities were detected at levels requiring characterization.

The stability data evaluated includes testing of 5 mg, 10 mg and 20 mg Clobazam Oral Films stored under ICH stability conditions at 25 °C ± 2 °C /60% RH ± 5% RH for 12 months and 40 °C ± 2 °C /75% RH ± 5% RH for 6 months. Overall, the stability data demonstrate acceptable chemical stability for up to 12 months when stored at 25 °C/60% RH and 40 °C/75% RH. The long-term trend analysis for the assays for each strength is projected to be within specification. **Based on the data submitted and in accordance with ICH Q1E, the proposed shelf-life of 24 months when stored at USP controlled room temperature is granted. The claim of categorical exclusion from environmental assessment based on 21 CFR 25.31(a) and 25.15(d) is acceptable.**

During manufacturing of Clobazam Oral Film; 5 mg, 10 mg, and 20 mg, (b) (4)

(b) (4)

strengths are compositionally proportional (b) (6) The Applicant commits to not reprocessing any batch without prior Agency approval of a supplement.

Clobazam content uniformity within the film is established (b) (4) and confirmed with (b) (4) monitoring (b) (4)

The Applicant follows microbial enumeration test methods provided in USP <61>/<62> with proposed specifications meeting requirements stated in USP <1111> for release and stability testing of the drug product. The data presented conforms to USP <1111> demonstrating absence of microbial or absence of microorganisms for all strengths. **The overall manufacturing inspection recommendation is approve based on all listed facilities being acceptable.**

Clobazam Oral Film is administered to the lingual surface for subsequent absorption through the gastrointestinal tract. Two bioavailability/bioequivalence studies [study 1895 (pilot) and study 162081 (pivotal)], with comparison to ONFI tablets, in healthy, non-smoking male and female volunteers under fasting conditions, are included as the required bridging studies for the submission of this 505(b)(2) NDA. In lieu of clinical bioavailability studies for the lowest strength (5mg), under provision of 21 CFR 320.22(d)(2), the Applicant requested biowaiver. **The biowaiver request for 5 mg strength is considered adequate provided the pivotal BE study is found acceptable by the OCP.**

The initial risk assessment identified dissolution as a high risk because “*Rapid release of the drug is needed to ensure active pharmaceutical ingredient is available for absorption once swallowed.*” Upon Biopharmaceutics review, factors that might reduce the final risk ranking for dissolution include:

1. All three strengths of the proposed product show very rapid dissolution ((b) (4)% cumulative mean drug release within (b) (4)min) in QC dissolution medium (surfactant not present).
2. The bio-strengths of the proposed product (10 mg and 20 mg) were administered without water during clinical trials, and demonstrated bioequivalence (BE, pending OCP review) to the reference drug product (ONFI tablets taken with 240 ml water). In addition, the observed Tmax values for the proposed product are comparable to those for the reference product. Thus, the risk of failure in product performance due to in vivo dissolution is low.
3. The Applicant did not test discriminating ability of the dissolution method for changes in API particle size using the final to-be-marketed drug product because such attribute is controlled (D90 of NMT (b) (4) μm), and it was previously demonstrated that the dissolution method is able to discriminate differences in API particle size (D90 of (b) (4) versus (b) (4) am) using an experimental formulation.

4. The API is likely to belong to BCS class I at the highest proposed strength, although BCS solubility for the drug substance should be interpreted with caution, since the products are instructed to be taken without liquid, and the saliva volume in the oral cavity is limited.
5. The 20 mg pilot batch (same formulation as the pivotal batch but manufactured at (b) (4) scale instead of (b) (4) commercial scale) showed **slower** release rate compared to pivotal batch (reached (b) (4)% mean release in (b) (4) minutes versus (b) (4) minutes), but resulted in **high** mean T/R ratio for Cmax of 110% at clinical study.

The proposed QC dissolution method is very similar to the dissolution method in the FDA “Dissolution Methods” database for clobazam tablets (ONFI tablets, reference product used in pivotal BE study). The Applicant demonstrated fast dissolution of the proposed product in various pH buffers (pH1.2, 4.5, 6.8, and water), so the decision to use 0.1N HCl as the dissolution medium was deemed acceptable. USP Apparatus V (paddle over disc) was chosen because it showed less variation in drug release compared to USP Apparatus I. The proposed dissolution method is considered acceptable.

The proposed acceptance criterion (Q = (b) (4)% in (b) (4) minutes) is considered too permissive. Based mainly on the in vitro dissolution profile data of the bio-batches, Q = (b) (4)% in 15 minutes was recommended to the Applicant. On 7/6/2018, the Applicant accepted the recommended dissolution acceptance criterion. The regulatory dissolution method and acceptance criteria are:

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Approved Acceptance criterion/criteria
V (Paddle over Disc), 56 mm opening, 40 mesh stainless steel*	75	0.1 N HCl	900	2, 6, 10, 15, 20, 30 min	Q = (b) (4)% in 15 minutes

*On 5/10/2018, in responding to Biopharm IR request, the Applicant clarified that the apparatus is “neither a true Apparatus II or a true Apparatus V because no specific apparatus exists for film products to date. The proposed setup utilizes two mesh discs secured within a ring to hold the film stationary which constitutes a slight departure from Apparatus V. The same Apparatus set up was used in the dissolution testing throughout development and is proposed to be used in the quality control dissolution method. The Sponsor has changed all nomenclature to Apparatus V.”⁴

C. Special Product Quality Labeling Recommendations

The product is intended for administration via adhesion to the tongue. **The product should not be swallowed whole or chewed.**

D. Final Risk Assessment



QUALITY ASSESSMENT



From Initial Risk Identification		Review Assessment		
Critical Quality Attribute	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Assay	Medium	In-process and end product testing	Acceptable	
Solid State	Medium	One known polymorph; No conversion observed during development	Acceptable	
Content Uniformity	Medium	In-process and end product testing	Acceptable	
Microbial Limits	Low	End product testing	Acceptable	
Dissolution	High	Method development and clinical experience demonstrate product is rapidly dissolving	Acceptable	
Palatability	Medium	Formulation includes suite of taste masking excipients	Acceptable	Evaluate formulation and manufacturing changes for impact
Disintegration	Medium	Information provided to demonstrate that variability in disintegration time does not affect pharmacokinetics of clobazam	Acceptable	Evaluate formulation and manufacturing changes for impact
Film Integrity	Medium	Formulated (b) (4) to ensure film integrity; End product testing monitors for visual defects; Variability in disintegration time does not impact pharmacokinetics	Acceptable	Evaluate formulation and manufacturing changes for impact
Particle Size	Low	Controlled in drug substance; Dissolution method sensitive to changes in particle size	Acceptable	
Film Adhesion	Medium	Formulation optimized to ensure appropriate adhesion as evidenced by clinical experience	Acceptable	Evaluate formulation and manufacturing changes for impact
Film Dimensions	Medium	Appropriate process controls and monitoring in place	Acceptable	
Water Content	Low	End product testing	Acceptable	

From Initial Risk Identification		Review Assessment		
Critical Quality Attribute	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Viscosity	Medium	In-process testing	Acceptable	Evaluate formulation and manufacturing changes for impact



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Wilson- Lee

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LABELING

{For NDA only}

R Regional Information

1.14 Labeling

Highlights of Prescribing Information

SYMPAZAN™ (clobazam) Oral Film, (b) (4) CIV Initial U.S. Approval: 2011
-----DOSAGE FORMS AND STRENGTHS-----

Oral Film: 5mg, 10mg and 20mg (3)

FULL PRESCRIBING INFORMATION: CONTENTS

3 DOSAGE FORMS AND STRENGTHS

(b) (4) SYMPAZAN™ (b) (4) :
5 mg film imprinted with C5
10 mg film imprinted with C10
20 mg film imprinted with C20

Reviewer's Assessment: Adequate

The recommended revisions are provided with tracked changes. The proprietary name and the established name, followed by dosage form and route of administration, and controlled substance symbol designating drug schedule are included in the highlight of prescribing information. A concise summary of the dosage and strength information is provided. These sections contain the appropriate statements consistent with the regulations 21 CFR 201.57. The referenced MonoSol Rx confirms to implement the finished dosage form nomenclature from Oral Soluble Film (OSF) to Oral Film (OF) following FDA comment that OSF is not considered an acceptable dosage form. Please see IR comment below.

Amendment (July 6, 2018)

IR Comment:

3. The proposed finished dosage form "oral soluble film" is not an acceptable dosage form as it does not comply with current USP Nomenclature Guidelines. The established name for this product is clobazam oral film. Revise all labels and labeling to include the acceptable finished dosage form – oral film. Please refer to the product using the appropriate established name in all future submissions and communications.

Aquestive Response

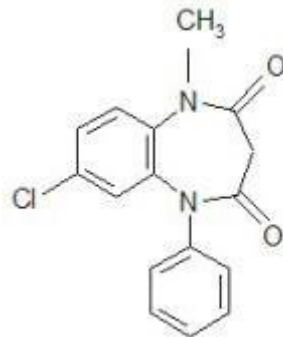
The Sponsor acknowledges the USP Nomenclature Guidelines and accordingly will revise all labels and labeling to reflect the acceptable finished dosage form of oral film and the established name "Clobazam Oral Film." The revised labels and labeling will be submitted to the NDA as soon as possible, but no later than the end of July.

Reviewer's Assessment of Response: Adequate

The revised label will be subject to review when submitted.

11 DESCRIPTION

(b) (4)



Clobazam is a white or almost white, crystalline powder with a slightly bitter taste; is slightly soluble in water, sparingly soluble in ethanol.

Each SYMPAZANTM Oral Film contains 5 mg, 10 mg or 20 mg of clobazam. The oral films also contain as inactive ingredients: citric acid, glycerol monooleate, hypromellose, maltitol, natural and artificial bitter masker, natural raspberry type flavor, artificial cooling flavor, polyethylene oxide, purified water, sucralose and sodium phosphate dibasic.

Reviewer's Assessment:

This section contains the appropriate statements consistent with the regulations 21 CFR 201.57. The elements that the description section must contain are included.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each SYMPAZANTM oral film is a white rectangular film that contains 5mg, 10 mg or 20 mg of clobazam and printed in black ink either "C5," "C10" or "C20" on the strip according to their respective strengths.

NDC 10094-205-60: 5 mg oral film, Package of 60 NDC

10094-210-60: 10 mg oral film, Package of 60 NDC 10094-

220-60: 20 mg oral film, Package of 60

Store oral films at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15-30°C (59-86°F). [See USP controlled room temperature.]

Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured by: Aquestive Therapeutics

Warren, NJ 07059

Reviewer's Assessment:

The information elements in the How supplied/storage and handling section are appropriate. The applicant has determined the (b) (4) based on studies (Section 3.2.P.7, Test Report 1632-009 of the NDA submission). The primary packaging configuration is designed to be (b) (4) effective. In accordance with recent draft guidance (b) (4) the applicant may wish to include (b) (4).

Immediate Container Label

{copy/paste or refer to a representative example of a proposed container label}



Reviewer's Assessment: Adequate

Firm has agreed to revise labeling to update dosage form to "oral film"

(b) (4)



Reviewer's Assessment: Adequate

Firm has agreed to revise labeling to update dosage form to "oral film"



Reviewer's Assessment: Adequate

Firm has agreed to revise labeling to update dosage form to "oral film"

{copy/paste or refer to a representative example of the proposed carton label here}

Reviewer's Assessment: Adequate

Firm has agreed to revise labeling to update dosage form to "oral film"



Reviewer's Assessment: Adequate

Firm has agreed to revise labeling to update dosage form to "oral film"

Reviewer's Assessment: Adequate

Firm has agreed to revise labeling to update dosage form to "oral film"

List of Deficiencies:

Primary Labeling Reviewer Name and Date:

***Milton J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div1/Branch III
6/31/2018***

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

***Wendy Wilson-Lee, PhD
Branch Chief***



QUALITY ASSESSMENT



OPQ/ONDP/Div1/Branch II

APPEARS THIS WAY ON ORIGINAL



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BIOPHARMACEUTICS

[IQA Review Guide Reference](#)

NDA/ANDA: NDA210833

Drug Product Name / Strength: Clobazam Oral Film (COF)¹/ 5 mg, 10 mg and 20 mg

Route of Administration: Oral

Applicant Name: MonoSol Rx, LLC

Review Recommendation: NDA210833 is adequate and is recommended for approval from Biopharmaceutics' perspective.

Review Summary:

Product Background:

Aquestive Therapeutics (name changed from MonoSol Rx LLC on 1/1/2018²) submits 505(b)(2) Original New Drug Application (NDA), 210833, for Clobazam Oral Film (COF) 5 mg, 10 mg and 20 mg strengths by relying on the prior safety and efficacy findings of the Agency for the Reference Listed Drug (RLD), ONFI[®] Oral Tablets CIV (NDA 202067, Lundbeck Pharmaceuticals LLC.). The proposed indication is as follows: "Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older." COF is administered to the lingual surface for subsequent absorption through the gastrointestinal tract. Two COF bioavailability/bioequivalence studies [study 1895 (pilot) and study 162081 (pivotal)], with comparison to ONFI tablets, in healthy, non-smoking male and female volunteers under fasting conditions, are included as the required bridging studies for the submission of this 505(b)(2) NDA. In lieu of clinical bioavailability studies for the lowest strength COF 5mg, under provision of 21 CFR 320.22(d)(2), the Applicant requested biowaiver. The COF 5 mg, 10 mg and 20 mg strengths are generated from a single (b) (4) formulation. During the manufacturing process, (b) (4)

(b) (4)

¹ On 7/6/2018, the Applicant agreed to change the name from Clobazam Oral Soluble Film (COSF) to Clobazam Oral Film (COF). See page 3 in <file:///C:/Cdsesub1/evsprod/NDA210833/0011/m1/us/12-cover-letter/cover-letter.pdf>

² <file:///C:/Cdsesub1/evsprod/NDA210833/0003/m1/us/12-cover-letter/cover-letter-0003.pdf>

(b) (4) The COF 5 mg, 10 mg, and 20 mg strengths are compositionally proportional (b) (4)

Risk assessment

The FDA's initial risk assessment for dissolution is high because "*Rapid release of the drug is needed to ensure active pharmaceutical ingredient is available for absorption once swallowed.*" Upon Biopharmaceutics review, factors that might reduce the final risk assessment for dissolution are summarized below.

1. All three strengths of the proposed product show very rapid dissolution ((b) (4)% cumulative mean drug release within (b) (4) min) in QC dissolution medium (b) (4).
2. The bio-strengths of the proposed product (10 mg and 20 mg) were administered without water during clinical trials, and demonstrated bioequivalence (BE, pending OCP review) to the reference drug product (ONFI tablets taken with 240 ml water). In addition, the observed Tmax values for the proposed product are comparable to those for the reference product. Thus, the risk of failure in product performance due to in vivo dissolution is low.
3. The Applicant did not test discriminating ability of the dissolution method for changes in API particle size using the final to-be-marketed drug product because such attribute is controlled (D90 of NMT (b) (4) μm), and it was previously demonstrated that the dissolution method is able to discriminate differences in API particle size (D90 of (b) (4) versus (b) (4) μm) using an experimental formulation.
4. The API is likely to belong to BCS class I at the highest proposed strength, although BCS solubility for the drug substance should be interpreted with caution, since the products are instructed to be taken without liquid, and the saliva volume in the oral cavity is limited.
5. The 20 mg pilot batch (same formulation as the pivotal batch but manufactured at (b) (4) scale instead of (b) (4) commercial scale) showed **slower** release rate compared to pivotal batch (reached (b) (4)% mean release in (b) (4) minutes versus (b) (4) minutes), but resulted in **high** mean T/R ratio for Cmax of 110% at clinical study.

QC dissolution method and acceptance criteria

The proposed QC dissolution method (Table 1) is very similar to the dissolution method in the FDA "Dissolution Methods" database for clobazam tablets (ONFI tablets, reference product used in pivotal BE study).

The Applicant demonstrated fast dissolution of the proposed product in various pH buffers (pH 1.2, 4.5, 6.8, and water), so the decision to use 0.1N HCl as the dissolution medium was deemed acceptable. USP Apparatus V (paddle over disc) was chosen because it showed less variation in drug release compared to USP Apparatus I. The proposed dissolution method is considered acceptable.

The proposed acceptance criterion (Q = (b) (4)% in (b) (4) minutes) is considered too permissive. Based mainly on the in vitro dissolution profile data of the bio-batches, Q = (b) (4)% in 15 minutes was recommended to the Applicant. On 7/6/2018, the Applicant accepted the recommended dissolution acceptance criterion³.

³ Page 1 in <file://Cdsesub1/evsprod/NDA210833/0011/m1/us/12-cover-letter/cover-letter.pdf>

Biowaiver

The Applicant submitted a biowaiver request for the 5 mg strength based on 21 CFR 320.22 (d)(2). The biowaiver request for 5 mg strength is considered adequate provided the pivotal BE study is found acceptable by the OCP (pending OCP review as of 07/10/2018).

Table 1. Summary of approved dissolution specification for finished product batch release and stability testing of all strengths of clobazam oral film

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times	Approved Acceptance criterion/criteria
V (Paddle over Disc), 56 mm opening, 40 mesh stainless steel*	75	0.1 N HCl	900	2, 6, 10, 15, 20, 30 min	Q ^(b) ₍₄₎ % in 15 minutes

*On 5/10/2018, in responding to Biopharm IR request, the Applicant clarified that the apparatus is “neither a true Apparatus II or a true Apparatus V because no specific apparatus exists for film products to date. The proposed setup utilizes two mesh discs secured within a ring to hold the film stationary which constitutes a slight departure from Apparatus V. The same Apparatus set up was used in the dissolution testing throughout development and is proposed to be used in the quality control dissolution method. The Sponsor has changed all nomenclature to Apparatus V.”⁴

Table 2. List of submissions being reviewed.

10/31/2017	NDA 210833/Original submission
5/10/2018	Responses to biopharmaceutics information request 1
7/6/2018	Responses to biopharmaceutics information request 2

Concise Description of Outstanding Issues Remaining: None

⁴ Response to FDA comment#4 in <file://Cdsub1/evsprod/NDA210833/0007/m1/us/112-other-corr/request-for-comments-and-advice.pdf>

BCS Designation

Table 3. API solubility

(a) Solubility included in the original submission⁵

Dissolution Media	SAM076
Water	0.108 mg/mL (97.2 mg/900 mL)
0.1N HCl	0.110 mg/mL (99.0 mg/900 mL)
pH 6.8	0.100 mg/mL (90.0 mg/900 mL)

(b) Solubility provided in IR response⁶

Media	Solubility
pH 1.2 0.1N HCl	0.134 mg/mL
pH 4.5 Acetate Buffer	0.133 mg/mL
pH 6.8 Phosphate Buffer	0.126 mg/mL

The Applicant did not formally request a BCS designation for the proposed drug product.

Reviewer’s Assessment:

The API at the highest proposed dose level (20 mg) is highly soluble (Table 3) per BCS definition. Based on information listed under “Permeability” section, the API is likely to be BCS class I. However, for the proposed product, cautious interpretation of BCS solubility is recommended. Please see details in “Solubility” section below.

Solubility:

Per proposed product label⁷, a daily dose greater than 5 mg should be administered in divided doses twice daily. Since the highest proposed daily dose is 40 mg, 20 mg will be the highest dose level at each time of dosing.

Per BCS definition of solubility, the API is highly soluble.

However, per proposed product label⁸, the product is not supposed to be administered with any liquid. The BCS solubility (highest strength is soluble in 250 mL or less of aqueous media) for the proposed product might have less relevance in predicting bioavailability, since volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to human volunteers with an 8 fluid ounce glass of water.

⁵ <file:///C:/cdsesub1/evsprod/NDA210833/0000/m5/53-clin-stud-rep/531-rep-biop-harm-stud/5313-in-vitro-in-vivo-corr-stud-rep/study-ard005/study-report-ard-005.pdf>

⁶ <file:///C:/cdsesub1/evsprod/NDA210833/0007/m1/us/112-other-corr/request-for-comments-and-advice.pdf>

⁷ <file:///C:/cdsesub1/evsprod/NDA210833/0003/m1/us/114-labeling/114a-draft-label/draft-labeling-text.pdf>

⁸ See “Important Administration Instructions” section in <file:///C:/cdsesub1/evsprod/NDA210833/0003/m1/us/114-labeling/114a-draft-label/draft-labeling-text.pdf>

Permeability:

Per product label of ONFI® Oral Tablets and suspension, “Clobazam is rapidly and extensively absorbed following oral administration..... (b) (4)

(b) (4).

(b) (4) Also, literature reported that “At least 87% of an oral dose is absorbed, as indicated by urinary recovery of labelled material.”⁹ Thus, it appears the API is highly permeable for absorption.

Dissolution: Please see section “Dissolution method and acceptance criteria” below.

Dissolution Method and Acceptance Criteria

(b) (4)

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Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Table 5. Summary of registration batches²¹

²¹ <file:///Cdsub1/evsprod/NDA210833/0000/m2/23-qos/regional-information.pdf>

Product (Product Code)	Bulk Film (Coating) Batch Number	Packaged Film Batch Number	Drug Substance Lot	Batch Use
COSF 5 mg (KY1RBM)	E16KX1-01	E16KY101-152	201505250162-15301	Registration/Stability
	E16KX1-02	E16KY102-154	201505250163-15301	Registration/Stability
	E16KX1-03	E16KY103-155	201505250164-15301	Registration/Stability
COSF 10 mg (KZ1RBM)	E16KX1-01	E16KZ101-152	201505250162-15301	Registration/Stability
	E16KX1-02	E16KZ102-154	201505250163-15301	Clinical/Registration/Stability
	E16KX1-03	E16KZ103-155	201505250164-15301	Registration/Stability
COSF 20 mg (LB1RBM)	E16LA1-04	E16LB104-155	201505250162-15301	Registration/Stability
	E16LA1-05	E16LB105-158	201505250163-15301	Registration/Stability
	E16LA1-06	E16LB106-158	201505250164-15301	Clinical/Registration/Stability

Table 6. Summary of clinical studies²²

Type of Study	Study Identifier	Report Location	Study Objective	Study Design	Test Products; Dosage Form; Route	No. of Healthy Volunteers (Gender, Age)	Duration of Treatment	Status; Type of Report
Phase 1 pilot BA study	1895	Module 5 Section 5.3.1.1 CSR 1895 Synopsis	Primary: PK – compare BA COSF vs RLD Secondary: safety and tolerability of COSF	Randomized, open label, single dose, 3-period, ¹ 4-arm, crossover, fasting only ≥21-day washout period	Test: COSF 5 mg COSF 20 mg Dosage form: soluble film Route: Oral RLD: Onfi 10 mg Onfi 20 mg Dosage form: tablet Route: oral	Safety population n = 16 Male n = 7 Female n = 9 Received ≥1 dose of COSF n = 15 Received ≥1 dose of Onfi n = 16 Age, years = 29–60	Single dose × 3	Complete; Abbreviated
Phase 1 pivotal BA/BE study	162018	Module 5 Section 5.3.1.2 CSR 162018 Synopsis	Primary: PK – compare BA COSF vs RLD Secondary: safety and tolerability of COSF	Randomized, open label, single dose, 4-period, ² 4-arm, crossover, fasting only ≥28-day washout period	Test: COSF- 10 mg COSF- 20 mg Dosage form: soluble film Route: oral RLD: Onfi 10 mg Onfi 20 mg Dosage form: tablet Route: oral	Safety population n = 51 Male n = 26 Female n = 25 Received ≥1 dose of COSF n = 50 Received ≥1 dose of Onfi n = 51 Age = 21–64 years	Single dose × 4	Complete; Full

BA/BE = bioavailability/bioequivalence; COSF = Clobazam Oral Soluble Film, MonoSol Rx; Onfi = Onfi (clobazam tablets), Lundbeck, Deerfield, IL;

PK = pharmacokinetics; RLD = Reference Listed Drug.

¹ Each subject was to receive a single dose of three of the four test products.

² Each subject was to receive a single dose of each of the four test products.

Source: Module 5, Module 5, Section 5.3.1.1 CSR 1895 and Section 5.3.1.2, CSR 162018.

Table 7. Summary of pivotal BE study

(a) Pivotal BE²³

²² In pilot BE study, batch information is the following: 5 mg COF (H15KM1-01); 20 mg COF (H15KN1-01)

²³ Page 8 in <file:///C:/cdsub1/evsprod/NDA210833/0000/m5/53-clin-stud-rep/531-rep-biopharm-stud/5312-compar-ba-be-stud-rep/study162018/162018-synopsis-fr.pdf>

Treatment Comparison	Parameter	Geometric LSM A	Geometric LSM B	Ratio ¹	90% Geometric C.I. ²		Intra-Subject Inter-Subject	
					Lower	Upper	CV	CV
COSF 20 mg (A) - ONFI® 20 mg (B)	AUC _{0-t}	10531.45	10152.24	103.74%	101.32%	106.21%	6.48%	24.63%
	AUC _{0-inf}	10712.10	10344.68	103.55%	101.16%	106.00%	6.41%	24.74%
	C _{max}	386.59	376.84	102.59%	95.43%	110.28%	20.05%	14.37%
		Geometric LSM C	Geometric LSM D					
COSF 10 mg (C) - ONFI® 10 mg (D)	AUC _{0-t}	4554.83	4583.30	99.38%	96.81%	102.02%	7.49%	25.76%
	AUC _{0-inf}	4714.55	4759.87	99.05%	96.72%	101.43%	6.79%	25.44%
	C _{max}	179.96	188.53	95.45%	90.19%	101.03%	16.29%	17.12%

COSF=Clobazam Oral Soluble Film

¹ Calculated using least-squares means according to the formula: e^(Difference) X 100.

² 90% Geometric Confidence Interval using ln-transformed data.

LSM: Least-Squares Mean

(b) Pilot BE (Treatment A: COF 5 mg, Treatment B: COF 20 mg, Treatment C: ONFI 10 mg, Treatment D: ONFI 20 mg)²⁴

Clobazam

Treatment A vs Treatment C

Pharmacokinetic Parameter	Test/Reference Ratio of Geometric Means (90% Confidence Interval)	Intra-Subject CV (%)
AUC _t	109.39% (102.14% – 117.16%)	7.98%
AUC _{inf}	109.62% (101.38% - 118.53%)	9.10%
C _{max}	112.22% (95.16% – 132.34%)	19.34%

Treatment B vs Treatment D

Pharmacokinetic Parameter	Test/Reference Ratio of Geometric Means (90% Confidence Interval)	Intra-Subject CV (%)
AUC _t	108.35% (101.92% – 115.19%)	7.98%
AUC _{inf}	108.70% (101.38% - 116.56%)	9.10%
C _{max}	109.60% (94.59% – 126.98%)	19.34%

Reviewer’s Assessment:

Two BA/BE studies (pilot and pivotal) were conducted (Tables 6&7). The pilot study (pilot batches manufactured using same formulation and process as registration batches but manufactured at (b) (4) scale instead of (b) (4) commercial scale) was conducted with roughly three times less subjects and using non-registration batches of COF 5 mg compared with 10mg ONFI tablet and 20 mg COF compared with ONFI 20 mg tablet²⁵. In pivotal BE study, registration batches of 10 and 20mg COF were compared with ONFI 10 and 20 mg tablets. The reported median Tmax for COF is 1 to 1.5 hour^{25,26}.

Note that the adequacy of BE is reviewed by OCP.

²⁴ Page 22 in <file://C:\cdsub1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\pilot-pk-study-1895\pilot-pk-study-1895.pdf>

²⁵ <file://C:\cdsub1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\pilot-pk-study-1895\pilot-pk-study-1895.pdf>

²⁶ <file://C:\cdsub1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study162018\162018-synopsis-fr.pdf>

Unlike ONFI tablets administered with 240 ml water, the proposed products were placed on the center of the tongue before swallowing without any additional water²⁷. In pivotal BE study, the observed median Tmax values (1.5 h for both strengths) are comparable to those from ONFI tablets (20mg: 2h; 10 mg: 1.5h). These observations indicate the dissolution of COF is not an issue even when no water was co-administered.

In pilot BE study, the same formulation as registration batches were used for test drugs of 5 (lot. H15KM1-01) and 20 mg (lot. H15KN1-01) strengths with median Tmax values of 1 and 1.5 h respectively. With 5 mg strength, the dissolution showed (b) (4) % mean release at (b) (4) minutes, whereas 20 mg strength showed slower release (reached (b) (4) % release was reached at (b) (4) minutes)²⁸.

Based on the information presented, dissolution of the proposed product is at a lower risk to impact the absorption of the API.

Note that in clinical studies for the proposed product, “*the subject was asked to rub the film gently with the tongue against the roof of the mouth to promote melting and disappearance of the film*”. However, no such instruction is included in the proposed label. Therefore the following email was communicated to OCP reviewer on 06/18/2018:

“Note that in clinical studies for the proposed product, *the subject was asked to rub the film gently with the tongue against the roof of the mouth to promote melting and disappearance of the film*”¹¹. From a Biopharmaceutics’ perspective, it is not clear whether this specific instruction to ensure adequate product disintegration (disappearance of the film) before the drug enters the esophagus is critical for product efficacy and/or safety, considering that no liquid will be co-administered with the Oral Soluble Film. Note also that such instruction is not included in the proposed draft product label. In addition, very young children (the product is proposed for patients 2 years of age or older) may not be able to follow such instruction (“*rub the film gently with the tongue against the roof of the mouth*”).”

The Applicant was asked under biopharmaceutics IR to provide clarification on whether the absence of such instruction in the labeling would or would not impact the in vivo performance of the drug product. On 7/6/2018, the Applicant justified how such instruction can be omitted from the label in response to IR2²⁹. The Applicant reiterated that “*the act of rubbing the film gently with the tongue against the roof of the mouth to promote melting and disappearance of the film was intended to further disintegration of the film and does not affect absorption*” and “*the variability in disintegration time does not affect the pharmacokinetics of clobazam.*”

From Biopharm’s perspective, given the pH-solubility profile data of clobazam (Table 3), and the fact that the saliva volume is approximately 1 mL at any given time, it is

²⁷ See “Drug Administration” section of [\\Cdsub1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study162018\162018-csr-fr.pdf](#)

²⁸ Pages 470-471 in [\\Cdsub1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\pilot-pk-study-1895\pilot-pk-study-1895.pdf](#)

¹¹ See “Drug Administration” section of [\\Cdsub1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study162018\162018-csr-fr.pdf](#)

²⁹ Pages 2-3 in [file://Cdsub1\evsprod\NDA210833\0011\m1\us\12-cover-letter\cover-letter.pdf](#)

logical to assume that upon film disintegration, the drug will not dissolve completely in the oral cavity; however, it is expected that drug will dissolve on exposure to gastrointestinal environment. Thus, the Biopharmaceutics Review Team defers to OCP, the final decision regarding the inclusion in the labeling of a recommendation to rub the film on the tongue against the roof of the mouth, as per the study protocol.

Application of dissolution/IVIVC in QbD

Reviewer's Assessment:

No IVIVC was conducted. Please also see section under dissolution method and criteria (Discriminating ability).

Bridging of Formulations

Reviewer's Assessment: Adequate

Pivotal clinical and registration batches were manufactured using the same formulation and process as proposed for commercial. Hence, bridging is not necessary.

Biowaiver Request

Table 8. Composition of final formulation of the proposed products³⁰

³⁰ Page 19 in [file:///C:/cdsesub1/evsprod/NDA210833/0000/m3/32-body-data/32p-drug-prod/clobazamorale \(b\) \(4\) ilm-oral \(b\) \(4\) ilm/32p2-pharm-dev/drug-product.pdf](file:///C:/cdsesub1/evsprod/NDA210833/0000/m3/32-body-data/32p-drug-prod/clobazamorale%20(b)%20(4)%20ilm-oral%20(b)%20(4)%20ilm/32p2-pharm-dev/drug-product.pdf)

Component	% Solids (w/w)	COSF 5 mg	COSF 10 mg	COSF 20 mg
(b) (4)	(b) (4)			(b) (4)
Polyethylene oxide				
¹ Maltitol				
Clobazam				
(b) (4) Natural Raspberry Type Flavor				
Hypromellose, (b) (4)				
(b) (4)				
Sucralose				
Sodium Phosphate Dibasic				
Citric Acid				
(b) (4) Artificial Cooling				
(b) (4) Natural & Artificial Bitter Masker				
Glycerol Monooleate (b) (4)				
Purified Water				
TOTAL (nominal % or mg)				
		(b) (4)		
1				
2				

Reviewer’s Assessment:

The biowaiver request for 5 mg proposed product is adequate provided pivotal BE study is found acceptable by the OCP (pending OCP’s decision on BE study see details below).

The Applicant submitted biowaiver request for 5 mg strength based on 21 CFR 320.22 (d)(2)³¹ to fulfill the following criteria:

(i) *The bioavailability of this other drug product has been measured.*

Pending OCP’s review.

Pivotal BE study was conducted for 10 and 20 mg proposed products, compared with 10 and 20 mg ONFI tablets. The adequacy of the study is under OCP’s purview. Also, note that per product label for ONFI tablets: “population pharmacokinetics analysis reveals pharmacokinetics of clobazam are linear from 5 mg/day to 160 mg/day”.

(ii) *Both drug products meet an appropriate in vitro test approved by FDA.*

Adequate.

The proposed QC dissolution method is adequate. The Applicant provided dissolution data for 5 mg (E16KY101-152, registration batch) and 10 mg (Biobatch used in pivotal

³¹ <file://Cdsesub1/evsprod/NDA210833/0000/m1/us/112-other-corr/request-for-waiver-of-in-vivo-bioavailability-studies.pdf>

BE study). Both strengths showed more than (b) (4)% mean release in (b) (4) minutes.³² The submitted data is acceptable and meet the criterion.

(iii) *The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients*

Adequate.

The compositions of COF 5 mg, 10 mg and 20 mg strengths are the same. COF 5 mg and 10 mg are compositionally proportional (b) (4). COF 5 mg, 10 mg, and 20 mg strengths are compositionally proportional (b) (4) (Table 8).

R Regional Information

Comparability Protocols

Reviewer's Assessment: N/A

Primary Biopharmaceutics Reviewer Name and Date:

Ho-Pi Lin

6/4/2018; 7/9/2018

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

Poonam Delvadia,

06/11/2018; 07/12/2018

Tertiary Reviewer Name and Date:

Gerlie Gieser, Ph.D. (for Ta-Chen Wu, Ph.D.) 7/12/2018

³² <\\Cdsub1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\studyard006\study-report-ard-006.pdf>

APPENDIX 1
Biopharmaceutics Information Requests and Applicant Responses

IR1 (sent on 4/26/2018)

1. Provide aqueous solubility of API in pH 4.5 and one that reflects the pH environment in oral cavity (e.g., pH 7.4).
2. Provide comparative dissolution profile data for your products in buffers covering the physiologic pH range (e.g. pH1.2, pH4.5, pH6.8, and pH7.4).
3. Justify the relevance of using 0.1 N HCl as your QC dissolution media given that the proposed drug product is intended to disintegrate and dissolve in the oral cavity.
4. It is noted that module 3.2.P.2. (Drug product) states use of ‘2 (paddle over disc)’, whereas module 3.2.P.5.2 states “Apparatus II (Paddle) with 56 mm, 40 mesh stainless steel discs used as sinkers” for dissolution testing. Clarify the specific USP apparatus (II or V) (1) was used for the dissolution testing and (2) is the proposed quality control (QC) dissolution method. Update relevant sections of your NDA submission accordingly.
5. In addition to the mean dissolution data presented in graphical and tabular formats, submit in the “Batch Analysis” section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the clinical/PK (pivotal and pilot) and registration/stability studies of all strengths in Microsoft Excel “.xls or .xlsx” format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions. Provide dissolution data as described in the example below.

Example - Reporting of individual vessel dissolution data

Cell A1 – Identifying Batch/Lot Label, and dissolution method/media used

	A	B	C	D	E	F	G	H	I	J
1	Test lot 12345 (QC method/QC media)									
2		1	2	4	6	8	10	12		
3	1	3	15	62	98	99	99	98		
4	2	3	15	64	94	92	95	95		
5	3	3	9	37	80	96	97	97		
6	4	4	13	44	79	97	98	99		
7	5	3	12	39	71	96	98	98		
8	6	3	14	60	98	97	99	99		
9	7	4	13	44	82	93	98	98		
10	8	5	22	89	97	98	97	97		
11	9	4	16	64	96	98	96	96		
12	10	4	14	57	98	96	99	99		
13	11	4	16	63	96	96	97	97		
14	12	6	22	87	96	93	96	96		
15										
16										
17										
18										
19										
20										
21										
22										

Cell A2 – blank

Individual Unit Number (starting from cell A3 numerical values signifying the test unit)

Use one sheet for each unique batch/lot. Label accordingly in cell A1

Sampling Times (starting from cell B2 numerical values indicating collection times (minutes or hours))

Dissolution Data (starting from cell B3 numerical values indicating percent drug release)

Sheet1 Sheet2 Sheet3

Follow the instructions provided in “**Specifications for File Format Types Using eCTD Specifications**” – updated March 2, 2017 (link below).

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf>

IR2 (sent on 6/28/2018)

1. Based on the submitted dissolution data of biobatch and exhibit/registration batches, it is recommended to tighten acceptance criterion to “Q = ^{(b) (4)}% in 15 minutes” for finished product batch release and stability testing of all strengths of your proposed product. Implement the above recommended dissolution acceptance criterion for your proposed product and update the drug product specification table and other relevant parts of your NDA accordingly.
Alternatively, for consideration of the wider proposed dissolution acceptance criterion (Q = ^{(b) (4)}% in ^{(b) (4)} minutes), data supported evidence can be submitted demonstrating that there is no impact of slower dissolution on in vivo performance of the proposed product.
2. In your pivotal comparative BA/BE clinical study (# 162018), the following instruction is described in the “Drug Administration” section (9.4.5.1): “*the subject was asked to rub the film gently with the tongue against the roof of the mouth to promote melting and disappearance of the film.*” Provide clarification whether the absence of such instruction in the labeling would or would not impact the in vivo performance of the drug product.



Poonam
Delvadia

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Ho-pi
Lin

Digitally signed by Ho-pi Lin
Date: 7/12/2018 04:52:03PM
GUID: 541b03f20004e3e4a074e1d5ff766104



Gerlie
Gieser

Digitally signed by Gerlie Gieser
Date: 7/12/2018 05:20:43PM
GUID: 507592ba00003d190b2ea34fe8fb8ccb



Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/27/2018 08:54:02AM
GUID: 50816dbc000085595ca3284bbca465a8

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/s/

HAROLD S SANO
11/05/2018