CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212640Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 212640

Review 1

Drug Product Name	Exservan™ (riluzole)
Dosage Form	Oral film
Strength	50 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Aquestive Therapeutics
US agent, if applicable	

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Suong (Su) Tran
Drug Product/Labeling	Mariappan Chelliah	Wendy Wilson-Lee
Manufacturing	Tianhong Tim Zhou	Nallaperumal Chidambaram
Microbiology	N/A	N/A
Biopharmaceutics	Kaushalkumar Dave	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s) Reviewed	Document Date	Discipline(s) Affected
SD-001, Original NDA	1/31/2019	All
SD-003, Response to 74-Day Letter comments	5/13/2019	All
SD-005, Response to IR	7/26/2019	Manufacturing
SD-006, Labeling/Container	8/28/2019	Labeling
SD-007, Response to IR	9/5/2019	Drug Product, Biopharmaceutics
SD-008/Labeling/Container	9/25/2019	Labeling
SD-009, Response to IR	10/1/2019	Biopharmaceutics
SD-009, Response to IR	10/1/2019	Biopharmaceutics

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II		(b) (4)	Adequate	3/6//2019	Reviewed by G. Ladouceur
	IV			Adequate [1]		
	III			N/A [2]		
	IV			N/A [2]		
	IV			N/A [2]		

[1] No updates to DMF since previous adequate review dated 9/22/2017.
[2] Adequate information provided in NDA.

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

Document	Application Number	Description
NDA	20599	Rilutek® (riluzole) tablets, Covis Pharma NDA referenced under 505(b)(2) to support safety and efficacy of riluzole.
IND	130939	Aquestive Therapeutics, development of riluzole oral film
NDA	209080	Italfarmaco S.p.A. NDA for Tiglutik™ (riluzole) oral suspension (competitor product). Approved 9/5/2018.
(b) (4)		

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **Approval** of NDA 212640 for Exservan™ (riluzole) oral film. The application, as amended in response to Agency information requests (IRs), 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

Aquestive Therapeutics developed Exservan (riluzole) oral film 50 mg as an alternative to Rilutek (riluzole) tablets for treatment of amyotrophic lateral sclerosis (ALS) in patients who have difficulty swallowing tablets.[1] The applicant requests approval of the product under a 505(b)(2) NDA that relies on the prior approval of Rilutek (NDA 20599). FDA granted Orphan designation for this product.

Riluzole oral film is designed to disintegrate rapidly when placed on the tongue and release the active ingredient as a solid suspended in saliva. Gastrointestinal absorption occurs through natural salivary drainage and intentional swallowing of saliva, followed by dissolution of riluzole in the stomach. The applicant identified (b) (4) as Subjective Attributes, not critical to quality or performance, but desirable for the finished drug product. Identity, appearance, assay, content uniformity, degradation, microbiological limits, (b) (4) elemental impurities, (b) (4), dissolution, and disintegration are identified as Quality Attributes that ensure performance of the drug product. The initial risk assessment identified palatability as a moderate risk attribute for the product.

Proposed indication(s) including intended patient population	Treatment of patients with amyotrophic lateral sclerosis (ALS).
Duration of treatment	Chronic
Maximum daily dose	100 mg
Alternative methods of administration	None

[1] Prior to the September 5, 2018 approval of Tiglutik™ (riluzole) oral suspension (NDA 209080, Italfarmaco S.p.A.), the only approved dosage form for riluzole was a conventional tablet.

B. Quality Assessment Overview

Drug Substance: **Adequate**

Riluzole is a well-characterized small molecule that is manufactured for the applicant by (b) (4) Information regarding manufacture and control of the bulk drug substance is incorporated by cross-reference to the manufacturer's DMF (b) (4) The DMF was reviewed and is deemed adequate to support approval of the NDA. Summary information submitted directly to the NDA, including general properties and the drug substance specification, is consistent with the information in the DMF and Riluzole USP monograph requirements.

Drug Product: **Adequate**

The proposed product is a polymer-based film matrix that contains 50 mg of riluzole per film. The formulation is similar to previous products developed by the applicant (e.g., Zuplenz® and Suboxone®); however, the riluzole oral film formulation incorporates polacrilex resin and flavors (b) (4) . The applicant evaluated the adequacy of the formulation's ability to mask riluzole's organoleptic effects in a pilot BA/BE study (Study No. 1897). There are no novel excipients and maximum daily exposures for excipients are within levels for FDA-approved products.

The proposed specification is adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product and batch-to-batch consistency through the product's lifecycle. The applicant has validated all non-compendial analytical methods used for testing the drug product. Acceptance criteria for impurities are consistent with ICH Q3B(R2) guidance and the USP monograph for riluzole tablets. The batch data provided for three registration batches demonstrate that the Applicant can manufacture the drug product with consistent quality.

Each riluzole oral film will be packaged in an aluminum foil pouch. The secondary container is a cardboard carton that contains 60 individually pouched riluzole oral films. The container closure system is adequate to maintain the product quality through the proposed shelf-life as demonstrated by the stability data. Up to 24 months of long-term stability data available for the three primary batches demonstrate the drug product is stable and no trending was noted for any of the quality attributes. **The proposed shelf-life of 24 months, when stored at controlled room temperature: 20°–25° (68°–77° F) is granted.**

Manufacturing: **Adequate**

The proposed commercial manufacturing process for Exservan is divided by the applicant into (b) (4)

(b) (4)

(b) (4) Critical process parameters for the proposed manufacturing process were optimized at (b) (4) kg batch scale and applied to five (b) (4) kg engineering batches (commercial scale).

All facilities involved in the manufacture and testing of Riluzole USP and Exservan (riluzole) oral film are currently acceptable.

Biopharmaceutics: **Adequate**

The proposed dissolution method for the proposed Riluzole Oral Film, 50 mg, is as follows: *900 mL of 0.1N HCl using USP Apparatus 1 (basket) at 50 rpm*. The provided dissolution data demonstrate that the proposed dissolution method can discriminate between the target product and a deviant batch prepared with (b) (4) content. However, the proposed method could not discriminate between the target and other deviant batches prepared with altered composition and process parameters. As the proposed product is designed to disintegrate very rapidly and the drug substance has high solubility in the proposed dissolution medium, development of a discriminating dissolution method is considered challenging. The applicant selected appropriate dissolution testing conditions for the product, and the provided data demonstrate some discriminating ability. Thus, the proposed dissolution method is deemed adequate for quality control testing of the proposed product. Based on the dissolution profile data from the clinical and registration batches and the data from discriminating ability studies, the proposed dissolution method is likely to be more discriminating, and thus be able to identify potential quality issues, if sampling is performed at an earlier time-point. Thus, it was recommended that the applicant revise the originally proposed dissolution acceptance criterion of '(b) (4)' to 'NLT (b) (4)% (Q) at 20 minutes.' The applicant agreed to the recommendation and revised the dissolution acceptance criterion accordingly. The revised dissolution acceptance criterion is deemed adequate for quality control testing of the proposed product.

Labeling: **Adequate**

The proposed labeling is deemed adequate from a quality perspective

Environmental: **Adequate**

The applicant submitted a claim for categorical exclusion under 21 CFR §25.31(a). Riluzole oral film is intended as an alternative to Rilutek tablets for the same indication (ALS), in the same patient population, and with the same dosing regimen. Approval of the application would not increase use of riluzole. **The claim for categorical exclusion is granted.**

Methods Verification:

Verification of analytical procedures submitted in the NDA by FDA laboratories was not requested during the review.

C. 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**	**Comments**
Assay, stability	Formulation, container closure, (b) (4), process parameters	**L**	(b) (4)	**Adequate**	
Content uniformity (CU)	Formulation, raw materials, process parameters, scale/equipment/site	**L**		**Adequate**	
Physical stability (solid state)	Formulation, raw materials, process parameters, scale/equipment/site	**L**		**Adequate**	
Microbial limits	Formulation, raw materials, process parameters, (b) (4) container closure	**L**		**Adequate**	
Dissolution	Formulation, raw materials, process parameters, scale/equipment/site	**L**		**Adequate**	
Palatability	Formulation, raw materials, container closure	**M**		**Adequate**	

From Initial Risk Identification			Review Assessment		
Attribute/CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Disintegration	Formulation, raw materials, process parameters, scale/equipment/site	**L**	(b) (4)	**Adequate**	
Film Integrity	Formulation, container closure, raw materials, process parameters, scale/equipment/site, (b) (4)	**L**			
Particle Size	Raw material particle size	**L**		**Adequate**	Particle size does not impact on dissolution profile.
Film Adhesion	Formulation, raw materials, process parameters, scale/equipment/site	**L**	N/A		Film only needs to adhere to tongue for brief period while it disintegrates (b) (4) Not a CQA
Film dimensions	Process parameters, scale/equipment/site	**L**	(b) (4)	**Adequate**	

D. List of Deficiencies for Complete Response: Not applicable.

Application Technical Lead Name and Date: Martha R. Heimann 10/16/2019.

28 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Exservan	adequate
Established name(s)	riluzole	adequate
Route(s) of administration	Oral	adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	50 mg	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	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.	n/a	n/a

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)	Apply EXSERVAN on top of the tongue where it adheres and dissolves. Do not administer with liquids. As the film dissolves, saliva should be swallowed in a normal manner, but the patient should refrain from chewing, spitting or talking.	adequate

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)	Oral film	adequate
Strength(s) in metric system	50 mg	adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	n/a
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	orange, rectangular-shaped, orally dissolving film with "R50" printed in white on one side.	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	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.	n/a	n/a

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Exservan (riluzole)	adequate
Dosage form(s) and route(s) of administration	Oral film	adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	n/a
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Edited to meet this requirement.	adequate
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.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	Riluzole is a member of the benzothiazole class.	adequate
Chemical name, structural formula, molecular weight	They are present.	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	Appearance and solubility statements are included.	adequate

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	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	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)	Oral film	adequate
Strength(s) in metric system	50 mg	adequate
Available units (e.g., bottles of 100 tablets)	Carton of 60 pouches	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	orange, rectangular-shaped film	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	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.	n/a	n/a

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.)	Protect from bright light.	Adequate
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	n/a
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)	adequate
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	n/a
Include information about child-resistant packaging	(b) (4)	adequate

1.2.5 Other Sections of Labeling

1.2.6 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	RILUTEK® is a registered trademark of Covis Pharmaceuticals Inc. Manufactured by: Aquestive Therapeutics Warren, NJ 07059	adequate

2.0 PATIENT LABELING

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

The storage and used instruction discussed in the "Instruction for Use" is adequate from the CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Exservan (riluzole) oral film	Adequate
Dosage strength	50 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	n/a
Net contents (e.g. tablet count)	60 oral films	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	10094-60	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	n/a	n/a
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Aquestive Therapeutics, Warren, NJ 07059	Adequate
Medication Guide (if applicable)	n/a	n/a
No text on Ferrule and Cap overseal	n/a	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	n/a
And others, if space is available	n/a	n/a

Assessment of Carton and Container Labeling: *Adequate*

1) Regarding the choice of term for describing the primary container closure: Per the data standard manuals:
   - PACKET: An envelope into which only one dose of a drug product, usually in the form of granules or powder, has been directly placed. An example includes glassine powder paper containing aspirin. Other examples include aluminum foil packets into which alcohol swabs and pledgets are placed.
   - POUCH: A flexible container used to protect or hold one or more doses of a drug product (e.g. a pouch into which oral contraceptive blister packs are inserted, and an overwrap pouch for large volume parenterals).

Based on the above definitions, the packaging term "pouch" as proposed by the Applicant is appropriate. This is also in alignment with some of the other approved products for film dosage form.

2) The "How To Use paragraph" on the carton has the following text: "Place film on top of tongue. Keep in place until film **dissolves**."

Technically, the film disintegrates and [redacted] (b) (4) stays as a suspension in the mouth. Therefore, the term “disintegrates” could be better choice of word instead of “dissolves”. However, “disintegrates” could be confusing to the patients. Furthermore, recently approved product from the same Applicant (NDA 210833 for Clobazam Oral Film.) uses the same text as proposed for this film. Therefore, the text as proposed by the Applicant is acceptable.

ITEMS FOR ADDITIONAL ASSESSMENT

n/a

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan Chelliah

Secondary Assessor: Wendy Wilson-Lee

Mariappan Chelliah

Digitally signed by Mariappan Chelliah
Date: 10/11/2019 11:10:11AM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 10/11/2019 01:18:45PM
GUID: 50816dbc000085595ca3284bbca465a8

25 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Application No: NDA 212640; 505(b)(2)
Drug Product Name/Strengths: Riluzole Oral Film/50 mg
Route of Administration: Oral
Indication: Treatment of Amyotrophic Lateral Sclerosis (ALS)
Applicant Name: Aquestive Therapeutics
Date of Submission: 01/31/2019 (Original)
Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Ta-Chen Wu, PhD

REVIEW SUMMARY

Submission: The proposed drug product, Riluzole Oral Film, 50 mg (designated as ROF by the Applicant during the development), is an orally dissolving (polymer based) film. This NDA is a 505(b)(2) submission which substantially relies on the prior safety and efficacy findings by the Agency for the Reference Listed Drug (RLD) Rilutek® tablets (NDA 020599, Covis Pharma) for the same indication 'Treatment of Amyotrophic Lateral Sclerosis (ALS)'.

Review Objective: The Biopharmaceutics review is focused on the evaluation of (1) the proposed dissolution method and acceptance criterion, and (2) formulation bridging.

Dissolution Method: The Applicant conducted various studies and provided justifications for selection of the suitable dissolution testing conditions. The proposed dissolution method for the proposed Riluzole Oral Film 50 mg is as follows: *900 mL of 0.1N HCl using USP Apparatus 1 (basket) at 50 rpm*. The Applicant prepared several test batches to investigate the discriminating ability of the proposed product. The provided dissolution data show that the proposed dissolution method can discriminate between the target product and the deviant batch prepared with (b) (4) content. However, the proposed method could not discriminate between the target and other deviant batches prepared with altered composition and process parameters. Considering that the proposed product is designed to disintegrate very rapidly, and that the drug substance has high solubility in the proposed dissolution medium, it is challenging to develop a discriminating dissolution method. Based on the Applicant's appropriate selection of the dissolution testing conditions, and the provided data demonstrating some discriminating ability, the proposed dissolution method is deemed adequate for quality control testing of the proposed product.

Dissolution Acceptance Criterion: Based on the provided full profile dissolution data from the clinical and registration batches, the Applicant's originally proposed dissolution acceptance criterion of '(b) (4)' was deemed permissive and, therefore, not acceptable. Note that the provided profile data from discriminating ability studies indicate that the proposed dissolution method is likely to be more discriminating and thus be able to identify potential quality issue with setting of dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 20 minutes' than with the currently proposed dissolution acceptance criterion of '(b) (4)

(b) (4)'. Therefore, the Applicant was recommended to implement the dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 20 minutes' for quality control testing of the proposed product. The Applicant agreed to the FDA's recommendation and revised the dissolution acceptance criterion accordingly.

The final and approved dissolution method and agreed-upon acceptance criterion for the quality control of the proposed drug product at batch release and during stability testing are as follows:

FDA approved dissolution method and acceptance criterion for the proposed product

Apparatus	USP Apparatus 1 (Basket)
Paddle Speed	50 rpm
Volume	900 mL
Medium	0.1N HCl
Temperature	37.0 ± 0.5 C
Acceptance Criterion	NLT (b) (4)% (Q) at 20 minutes

Formulation Bridging: In-vitro or in-vivo bridging study is not needed for the proposed product, as there were no changes made in (i) composition for the clinical batches, exhibit batches, and proposed commercial drug product, (ii) product manufacturing site, and (iii) manufacturing process in the scale-up.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 212640 for Riluzole Oral Film, 50 mg, is adequate and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	01/31/2019	Original NDA Submission
0003	05/13/2019	Quality/Response to Information Request
0007	09/05/2019	Quality/Response to Information Request
0009	10/01/2019	Quality/Response to Information Request
0010	10/07/2019	Quality/Response to Information Request

BACKGROUND

The proposed drug product, Riluzole Oral Film, 50 mg (designated as ROF by the Applicant during the development), is an orally dissolving (polymer based) film dosage form of riluzole. This NDA substantially relies on the prior safety and efficacy findings of the Agency for the Reference Listed Drug (RLD) Rilutek® tablets (NDA 020599, Covis Pharma). The proposed indication for ROF is identical to the indication approved for the RLD Rilutek® 50 mg tablets: 'For the treatment of amyotrophic lateral sclerosis (ALS).' The mechanism by which riluzole exerts its therapeutic effects in patients with ALS is unknown.

The proposed product is a 'convenience dosage form' intended to offer compliance to the ALS patients as swallowing of a tablet can be challenging in such patient population. ROF contains the active ingredient riluzole incorporated into a polymer-based film matrix utilizing Aquestive Therapeutics' PharmFilm® technology. The film (b) (4) is intended for application on top of the tongue where it disintegrates and releases (b) (4) riluzole into the saliva which is then swallowed for gastrointestinal (GI) absorption.

The Sponsor/Applicant conducted two in vivo studies with ROF to evaluate the bioavailability (BA)/pharmacokinetics (PK) of riluzole in healthy volunteers (pilot Study 1897 and pivotal Study 162020). The results of these studies will be reviewed by the Office of Clinical Pharmacology.

Study 1897 was a pilot, open-label, randomized, single-dose, 3-period, 4-arm, crossover, comparative organoleptic effect and bioavailability study of ROF 50 mg and Rilutek Tablet 50 mg in healthy male and female volunteers under fasting conditions. The objectives of this study were to assess the organoleptic effect of ROF 50 mg administered with or without water compared to that of crushed Rilutek Tablet 50 mg administered with applesauce, as well as to evaluate comparative BA between ROF 50 mg administered with and without water and intact Rilutek 50mg Tablet administered with water.

Study 162020 was a pivotal, open-label, randomized, single-dose, 5-period, 4-arm, crossover, comparative BA study conducted under fasting conditions in healthy volunteers. The primary objective of this study was to evaluate the comparative BA of riluzole ROF 50 mg and Rilutek

Tablets 50 mg in healthy, non-smoking male and female volunteers and to investigate the potential food effect for ROF 50 mg.

The Biopharmaceutics review is focused on the evaluation of the 1) proposed dissolution method and acceptance criteria, and (2) formulation bridging, as presented below.

Dissolution Method Development: General Biopharmaceutics comments related to the dissolution method, acceptance criterion and data submission were provided to the Applicant with the Pre-IND (#130939)Written Responses letter issued July 21, 2016.

The Applicant's originally proposed dissolution method and acceptance criterion are as follow:

Table 1: Applicant's originally proposed Dissolution Method and Acceptance Criterion for Riluzole Oral Film/50 mg

Apparatus	USP Apparatus 1 (basket)
Paddle Speed	50 rpm
Volume	900 mL
Medium	0.1N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criteria	NLT (b) (4)% (Q) in (b) (4)

Drug Solubility: In the original submission, the Applicant provided solubility data of riluzole in water, pH 6.8 phosphate buffer and 0.1 N HCl, but not in pH 4.5 condition. Therefore, the Applicant was recommended (via an IR sent on 04/12/2019) to provide this information. Also, the Applicant had provided only the mean solubility values but not the detailed methodology for the multimedia solubility studies. The Applicant was recommended (via an IR sent on 08/07/2019) to provide the detailed methodology for the multimedia solubility studies performed with riluzole and to provide the solubility data as mean ± SD from replicates (e.g., n=3-6). In response (dated 09/05/2019), the Applicant provided the requested information/data.

The Applicant's provided solubility data indicate that riluzole has high solubility (20 mg/mL) in 0.1N HCl in comparison to other physiological conditions where the solubility remains nearly unchanged at 0.4 mg/mL (Table 2).

Table 2: Solubility of riluzole in aqueous media

Media	24 Hours at 37°C			48 Hours at 37°C		
	Solubility (mg/mL)	Average Solubility (N = 3) (mg/mL)	Standard Deviation (SD)	Solubility (mg/mL)	Average Solubility (N = 3) (mg/mL)	Standard Deviation (SD)
Water	0.41	0.42	0.01	0.42	0.41	0.01
	0.41			0.40		
	0.43			0.41		
pH 6.8 Buffer	0.39	0.42	0.04	0.39	0.39	0.01
	0.41			0.40		
	0.46			0.39		
pH 4.5 Buffer	0.49	0.46	0.05	0.47	0.47	0.01
	0.48			0.47		
	0.40			0.48		
0.1N HCl	19.65	19.82	0.31	20.01	20.28	0.42
	20.18			20.76		
	19.63			20.07		

Dissolution Testing Conditions/Parameters: For selection of the dissolution testing conditions, the Applicant performed several studies as described below.

(b) (4)

Discriminating Ability of the Dissolution Method

In the original submission, the Applicant did not provide any data demonstrating the discriminating ability of the proposed dissolution method. Therefore, the Applicant was recommended (via an IR sent on 04/12/2019) to provide the list of CMAs and CPPs that may affect the dissolution of the proposed product and to demonstrate the discriminating ability of the proposed method towards these attributes.

In response (dated 05/13/2019), the Applicant provided limited information/data where the discriminating ability of the proposed method was investigated by comparing the dissolution

of test ROF prepared with drug substance from two different API suppliers (b) (4) (b) (4) against the Listed Drug product 'Rilutek' (Figure 3).

Figure 3. Dissolution of ROFs Made with (b) (4) vs. (b) (4) API

The provided data were insufficient and inconclusive to support the discriminating ability of the proposed dissolution method. Therefore, the following IR was sent to the Applicant on 08/07/2019:

*"**1.** The provided information in your original submission and in your response (dated 05/13/2019) to the Biopharmaceutics information request indicate that the discriminating ability of the proposed dissolution method is not adequately investigated/demonstrated. Clarify how the test products (F15KF1-01 and J15KF1-01) specified in the Figure 2 for 'Dissolution of ROFs Made with (b) (4) vs. (b) (4) API' in the Module 3.2.P.2 Pharmaceutical Development report were different from each other and from the target product with regards to the drug substance particle size. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles between the reference drug product (i.e., target/proposed product; not the Listed Drug) and test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± 10-20% change to the specified values or ranges for these variables). In addition, the limited dissolution data provided in the submission suggest that there is no significant difference in the dissolution profiles of the studied test products, which does not support your conclusion that the proposed dissolution method is discriminating towards the drug substance particle size. Please provide explanation for your conclusion with supporting information/data.*

2. *We recommend that you investigate the discriminating ability of the proposed dissolution method not only towards a meaningful change in the drug substance particle size, but also towards meaningful change in the CMAs, CPPs and CFVs, such as* (b) (4) (b) (4)*, change in the composition of the proposed product, etc.*

3. *Provide complete multi-point dissolution profile data for each variable tested during the method development and assessment of discriminating ability, with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products [individual (n=12), mean, SD, % CV at each time point and mean profiles]. In addition, if available, submit data showing that the selected dissolution method can reject product that is not bioequivalent to the reference-target drug product."*

In response (dated 09/05/2019), the Applicant acknowledged that the proposed dissolution method is not discriminating with respect to the API particle size. The Applicant argued that (b) (4); however, since the solubility of riluzole in 0.1N HCl dissolution medium (simulated conditions for gastric fluid) is high, the dissolution is rapid with respect to the particle sizes evaluated and hence the method is unable to discriminate between the dissolution profiles.

As part of the response to the FDA's IR, the Applicant investigated the discriminating ability of the proposed dissolution method using variant batches, as shown in Table 3, and provided full profile dissolution data.

Table 3: Films with Different Formulation Parameters

Film Lot No.	Parameter
6-1-3	(b) (4)
6-1-3 ((b) (4)	
6-1-3 (	
6-1-2	
6-2-2	
9-1-1	
10-1-1	
11-1-1	
12-1-1	

The Applicant claimed that the proposed method has the discriminating ability towards a critical formulation variable [with a batch named '11-1-1' which was prepared with (b) (4) content] and a critical process parameter [with a batch named '6-1-3 (b) (4)' which was prepared with (b) (4) content in the film]. Per the FDA's request, detail for how these

deviant batches differ from the target product was provided on 10/07/2019 (See Appendix 1). The comparative dissolution data for these deviant batches and the target batch are presented in Figure 4 and Figure 5.

Figure 4. Dissolution profiles of the test batches prepared to demonstrate the discriminating ability of the proposed dissolution method

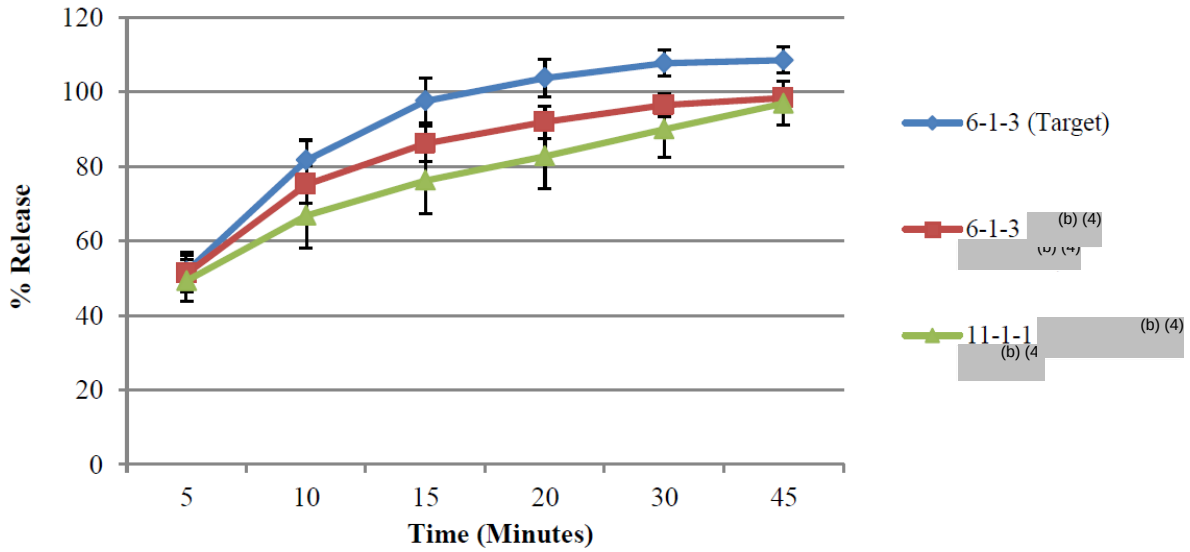
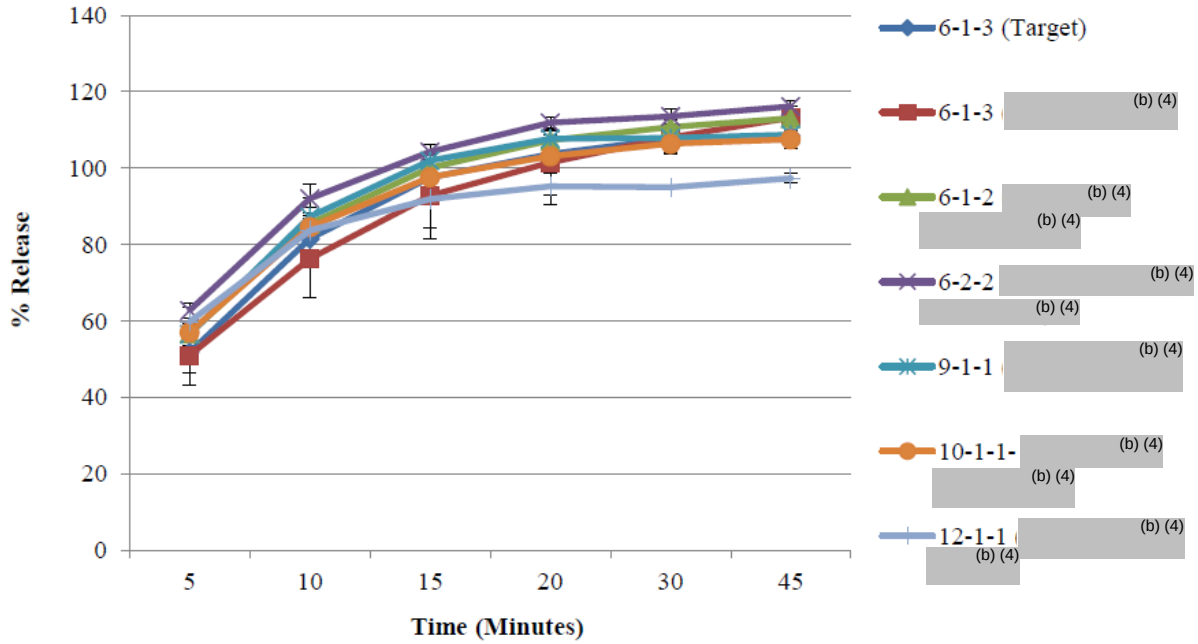


Figure 5. Dissolution profiles of the test batches prepared to demonstrate the discriminating ability of the proposed dissolution method



Reviewer's Assessment: [redacted] The Applicant's selection of 0.1N HCl as the dissolution medium for further investigation is adequately justified [redacted] The Applicant's selection of USP Apparatus 1 for the dissolution testing is appropriate [redacted]. The Applicant did not provide any data justifying the selection of the stirring rate; however, the proposed stirring rate (50 rpm) with USP Apparatus 1 is considered optimal and therefore acceptable for the proposed product. The provided data support the selection of the proposed dissolution method for further investigation of discriminating ability of the method.

The Applicant prepared several test batches to investigate the discriminating ability of the proposed product (Table 3). The Applicant appropriately selected the critical attributes/variables to test the discriminating ability of the proposed product. The Applicant provided full profile dissolution data for all variant batches. The provided dissolution data show that the proposed dissolution method can discriminate between the target product (6-1-3 target) and the deviant batch '11-1-1 [redacted]' with similarity factor (f2) value of 41. However, the proposed method could not discriminate between the target and other deviant batches (Figure 5). The provided comparative dissolution data show that the proposed method is likely to discriminate between the target product and the product with [redacted] as the f2 value of 50 for comparative dissolution data from the target product and the deviant batch prepared with [redacted] can be considered to be at the borderline.

Considering that the proposed product is designed to disintegrate very rapidly, and that the drug substance has very high solubility in the proposed dissolution medium, it is challenging to develop a discriminating dissolution method. The Applicant has adequately attempted to demonstrate the discriminating ability of the proposed dissolution method. Based on the Applicant's appropriate selection of the dissolution testing conditions, and the provided data from discriminating ability studies, this Reviewer determines that the proposed dissolution method is adequate for quality control testing of the proposed product.

Dissolution Acceptance Criterion:

In the original submission, the Applicant stated that all individual vessel dissolution data for the clinical and registration/stability batches are provided in the Module 3 supporting document "Riluzole Dissolution Data – Individual Vessel with Graphs". However, the full profile dissolution data for the zero-time/batch-release for the clinical and registration batches were not provided in the mentioned file and were subsequently requested (via an IR sent on 04/12/2019). The Applicant provided the requested data on 05/13/2019. Based on the provided full profile dissolution data from the clinical and registration batches, the Applicant's originally proposed dissolution acceptance criterion of '(b) (4)' was deemed permissive and therefore not acceptable. Also, the provided data from discriminating ability studies indicate that the proposed dissolution method is likely to be more discriminating at earlier time-point (Figure 4), and thus to be able to detect potential quality issue, with the dissolution acceptance criterion being set as 'NLT (b) (4)% (Q) at 20 minutes'. Based on the provided information/data, the Applicant was recommended (via an IR sent on 09/26/2019) to implement the dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 20 minutes' for quality control testing of the proposed product. In response (dated 10/01/2019), the Applicant accepted the FDA's recommendation and revised the dissolution acceptance criterion. The FDA's approved dissolution method and acceptance criterion for the proposed product are described in Table 4.

Table 4: FDA approved dissolution method and acceptance criterion for the proposed Riluzole Oral Film/50 mg

Apparatus	USP Apparatus 1 (basket)
Paddle Speed	50 rpm
Volume	900 mL
Medium	0.1N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criteria	NLT (b) (4)% (Q) in 20 minutes

(b) (4)

(b) (4)

(b) (4)

(b) (4) the Applicant's proposal to exclude this test from the finished product specifications is acceptable.

Formulation Bridging: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the pivotal clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 10/10/2019 02:20:56PM
GUID: 508da6df000269e151ff37cd8f4e13a1

Kaushalkumar Dave

Digitally signed by Kaushalkumar Dave
Date: 10/10/2019 09:15:04AM
GUID: 5575db68006e2262805f2e6449c54250

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAHLIA A WALTERS
10/17/2019 06:57:19 AM