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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Rainer W. Paine, MD, PhD
NDA 212640
Exservan (Riluzole Oral Film)

CLINICAL REVIEW

Application Type	505 (b)(2)
Application Number(s)	212640
Priority or Standard	Standard
Receipt Date(s)	01/31/2019
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Division/Office	Division of Neurology Products
Reviewer Name(s)	Rainer W. Paine, MD, PhD
Review Completion Date	10/08/19
Established Name	Riluzole Oral Film
(Proposed) Trade Name	Exservan
Applicant	Aquestive Therapeutics
Formulation(s)	Oral Film, 50 mg of riluzole
Dosing Regimen	50 mg every 12 hours
Applicant Proposed Indication(s)/Population(s)	Amyotrophic lateral sclerosis (ALS)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Amyotrophic lateral sclerosis (ALS)

Table of Contents

Glossary.....	4
1. Executive Summary	6
1.1. Product Introduction.....	6
1.2. Conclusions on the Substantial Evidence of Effectiveness	6
1.3. Benefit-Risk Assessment	7
2. Therapeutic Context	7
2.1. Analysis of Condition.....	7
2.2. Analysis of Current Treatment Options	7
3. Regulatory Background	8
3.1. Summary of Presubmission/Submission Regulatory Activity	8
3.2. Foreign Regulatory Actions and Marketing History.....	8
4. Sources of Clinical Data and Review Strategy	9
4.1. Table of Clinical Studies.....	9
4.2. Review Strategy.....	10
5. Review of Relevant Individual Trials Used to Support Efficacy	10
6. Review of Safety	10
6.1. Safety Review Approach	10
6.2. Review of the Safety Database	11
6.2.1. Overall Exposure	11
6.2.2. Adequacy of the Safety Assessments	11
6.3. Safety Results	11
6.3.1. Deaths, Serious Adverse Events, and Significant Adverse Events.....	11
6.3.2. Dropouts or Discontinuations Due to Adverse Effects	11
6.3.3. Adverse Events.....	11
6.3.4. Laboratory Findings	12
6.3.5. Vital Signs	12
6.3.6. Swallowing Study 17MO1R-0012.....	13
6.4. Safety in the Postmarket Setting.....	14
CDER Clinical Review Template	2
<i>Version date: September 6, 2017 for all NDAs and BLAs</i>	

Clinical Review

Rainer W. Paine, MD, PhD

NDA 212640

Exservan (Riluzole Oral Film)

6.4.1. Safety Concerns Identified Through Postmarket Experience.....	14
6.5. Integrated Assessment of Safety	14
7. Labeling Recommendations	14
7.1. Drug Labeling.....	14
8. Appendices	15
8.1. References.....	15

Table of Tables

Table 1: Table of Clinical Studies.....	9
Table 2: Treatment-Emergent Adverse Events and Number of Events Summarized per Treatment. Source: Study 162020 CSR	12
Table 3: Penetration Aspiration Scale (PAS). VF = Vocal Folds	13

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BA/BE	bioavailability and bioequivalence
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

Clinical Review

Rainer W. Paine, MD, PhD

NDA 212640

Exservan (Riluzole Oral Film)

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PeRC	Pediatric Review Committee
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
ROF	riluzole oral film
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

This application is for Exservan[®], a new oral film formulation of riluzole. Riluzole (Rilutek[®], 50 mg tablets) was approved for the treatment of patients with amyotrophic lateral sclerosis (ALS) in 1995 under NDA 020599. The indication for riluzole oral film (ROF) is proposed to be the same as Rilutek[®], treatment of patients with ALS. This application is a 505 (b)(2) application based on bioavailability and bioequivalence (BA/BE) studies to bridge the safety and efficacy of the new oral film formulation to the Reference Listed Drug (RLD), Rilutek[®] tablet.

The recommended dosage for riluzole is 50 mg taken orally twice daily. A single unit of the oral film formulation of riluzole will provide an equivalent dose to the 50 mg tablet. Oral administration of the new formulation is by manual placement of the film on the top of the tongue. The film will then dissolve and be swallowed with saliva. Dilution with liquids is not necessary. The applicant purports that this dosage form will be easier to administer to ALS patients with oropharyngeal dysphagia because it would eliminate the need to crush Rilutek[®] tablets to powder and combine them with liquid.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This is a 505 (b)(2) application based on a pivotal bioavailability and bioequivalence study to bridge the safety and efficacy of the new oral film formulation to the approved tablet dosage form of riluzole.

The Office of Clinical Pharmacology review team has reviewed the results of this pivotal bioequivalence study (Study 162020) and recommends approval based on the bioequivalence demonstrated between 50 mg EXSERVAN[®] oral soluble film and the listed drug RILUTEK[®] oral tablet 50 mg (refer to Clinical Pharmacology Review).

1.3. **Benefit-Risk Assessment**

The overall benefit-risk assessment of the new oral film formulation of riluzole is unchanged from the approved tablets. Although oral hypoesthesia was observed after the administration of riluzole oral film (38%), there was no adverse effect on swallowing.

2. **Therapeutic Context**

2.1. **Analysis of Condition**

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal motor neuron disease. It is characterized by the gradual degeneration and death of the motor neurons responsible for voluntary control of muscles.

ALS patients become progressively weaker, losing the ability to move their bodies. Respiratory muscles are also affected, leading to respiratory failure and the death of most patients within 3 to 5 years from the onset of symptoms. Approximately 10 percent of ALS patients survive for 10 or more years. Shorter survival is associated with older age at onset, bulbar onset, and faster rate of respiratory dysfunction.

The incidence of ALS is 2 per 100,000 per year with approximately 6000 new cases per year in the U.S. The estimated prevalence in the U.S. is 5 per 100,000 population with approximately 16,000 cases. ALS most frequently affects people between 40 and 70 years of age (median age 55).

2.2. **Analysis of Current Treatment Options**

There is no cure for ALS. Most available treatments are intended to relieve symptoms, such as cramps and spasticity, and improve the quality of life. There are two FDA-approved treatments for ALS: riluzole (Rilutek), which prolongs survival by about 3 months and extends the time before ventilatory support is needed; and edaravone (Radicava), which demonstrated a 33% smaller functional decline compared to placebo after 24 weeks in patients within 2 years of diagnosis and with a forced vital capacity (FVC) of at least 80%. A new formulation of riluzole (Tiglutek oral suspension, NDA 209080) was approved in September 2018 through the 505(b)(2) pathway.

3. Regulatory Background

3.1. Summary of Presubmission/Submission Regulatory Activity

Type B Pre-IND written responses were sent to the applicant on July 21, 2016. Clinical issues discussed included the need for assessment of chronic local oral cavity irritation in clinical studies and the need to assess swallowing in ALS patients after dosing with riluzole oral film. The applicant was also advised of the need to conduct a single dose, fasted state bioavailability/bioequivalence study and to evaluate food effect.

IND 130939 for riluzole oral film in ALS was allowed to proceed on December 23, 2016.

On November 22, 2017 the Pediatric Review Committee (PeRC) concurred with the initial pediatric study plan (iPSP) and the sponsor's plan for a full waiver of pediatric studies.

Type C written responses were sent to the applicant on March 21, 2018. The applicant was informed that a type 505(b)(2) NDA appeared acceptable and that the final study report for the swallowing study (17MO1R-0012) would need to be included in the NDA submission. The applicant was also advised that Study 17MO1R-0016 to assess chronic oral cavity irritation would not be needed because the adverse events reported for the pivotal BA/Food Effect Study 162020 included only oral hypoesthesia and erythema with no other concerning findings of oral cavity irritation.

(b) (4)

On September 11, 2018, the applicant requested early termination of the swallowing study (17MO1R-0012) after interim analysis showed no adverse effect on swallowing from ROF. The Division granted the request on September 12, 2018.

3.2. Foreign Regulatory Actions and Marketing History

Riluzole oral film (Exservan®) is not approved or marketed in any country.

4. Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

Table 1: Table of Clinical Studies

Type of Study	Study ID	Study objective	Study design	Study drug, dose, route of administration	No. of subjects	Healthy subjects or diagnosis of patients	Treatment duration
Phase 1 Pilot BA/BE and Organoleptic Effect Study	1897	PK and Organoleptic Effect	Open-label, randomized, single-dose, 3-period, 4-arm, crossover, comparative bioavailability study under fasting conditions in healthy volunteers.	Test: ROF 50 mg RLD: RILUTEK® 50 mg oral tablet	16	Healthy Subjects	Single doses x3, 7-day washout between doses
Phase 1 Pivotal BA/BE Study	162020	Primary: PK Secondary: Safety and Tolerability	Open-label, randomized, single dose, five-period, replicate, crossover, comparative bioavailability study under fasting conditions in healthy volunteers. Subjects randomized to receive ABABC and BABAC.	Test: ROF 50 mg RLD: RILUTEK® 50 mg oral tablet Regimen: A = 1 x 50 mg ROF without water under fasting conditions B = 1 x 50 mg Rilutek + 240 mL of water under fasting conditions C = 1 x 50 mg ROF without water following a standardized high-fat meal	Enrolled = 32 Completed = 30	Healthy Subjects	Single doses x5, 7-day washout between doses

Type of Study	Study ID	Study objective	Study design	Study drug, dose, route of administration	No. of subjects	Healthy subjects or diagnosis of patients	Treatment duration
Phase 2 Safety	17M01R-0012	Swallowing Safety and Tolerability	Open-label, single-center, single-dose, safety and tolerability study	Test: ROF 50 mg	9	Subjects with ALS	1 Visit

4.2. Review Strategy

This review only includes the safety review of the new riluzole oral film formulation.

5. Review of Relevant Individual Trials Used to Support Efficacy

This section is not applicable because this application is a 505 (b)(2) application based on a bioequivalence study to bridge the safety and efficacy of the new oral film formulation to the approved tablet dosage form. The applicant is relying on efficacy data from the already-approved RLD Rilutek (NDA 020599). The applicant has not conducted any studies of efficacy.

6. Review of Safety

The review of safety evaluated the three studies conducted by the applicant: pilot study 1897, pivotal study 162020, and swallowing safety study 17M01R-0012.

6.1. Safety Review Approach

The review attempted to identify any new safety signals from the submitted studies that could change the current safety profile of riluzole.

6.2. Review of the Safety Database

6.2.1. Overall Exposure

Forty-eight healthy volunteers were exposed to ROF 50mg in the pilot (n=16) and pivotal (n=32) studies. A total of 146 doses of ROF were administered to healthy volunteers (as well as 85 doses of Rilutek). In addition, 9 patients with ALS were exposed to one dose each of 50 mg ROF in the swallowing study (17M01R-0012).

6.2.2. Adequacy of the Safety Assessments

The applicant's safety assessments for this 505(b)(2) application appeared adequate.

The clinical safety assessments included treatment-emergent adverse events, vital signs, and laboratory assessments.

6.3. Safety Results

6.3.1. Deaths, Serious Adverse Events, and Significant Adverse Events

None.

6.3.2. Dropouts or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations in any of the three ROF clinical studies due to adverse effects.

6.3.3. Adverse Events

There were four adverse events in the pilot study 1897: two subjects with sleepiness in the ROF group and one subject with sleepiness and one with nausea in the Rilutek group. Adverse events from Study 162020 are shown in Table 2, copied from the submission and verified from the submitted data. Oral hypoesthesia occurred in both the fasting and fed riluzole oral film groups (38% and 10%, respectively) but not with Rilutek tablets. The intensities of the adverse events were mild. There were no adverse events reported for the swallowing safety and tolerability study 17M01R-0012.

Table 2: Treatment-Emergent Adverse Events and Number of Events Summarized per Treatment. Source: Study 162020 CSR

MedDRA® System Organ Class MedDRA® Preferred Term	Statistic	Riluzole 50 mg Oral Soluble Film Fasting Conditions (N=32)	RILUTEK® 50 mg Tablet Fasting Conditions (N=31)	Riluzole 50 mg Oral Soluble Film Fed Conditions (N=30)	Overall (N=32)
Number of TEAEs	E	23	8	13	44
Number of Subjects with TEAEs	n (%)	15 (46.9)	7 (22.6)	8 (26.7)	19 (59.4)
Gastrointestinal disorders	n (%) E	13 (40.6) 14	0	3 (10.0) 3	15 (46.9) 17
Hypoaesthesia oral	n (%) E	12 (37.5) 13	0	3 (10.0) 3	14 (43.8) 16
Oral mucosal erythema	n (%) E	1 (3.1) 1	0	0	1 (3.1) 1
Nervous system disorders	n (%) E	5 (15.6) 7	6 (19.4) 6	3 (10.0) 3	10 (31.3) 16
Somnolence	n (%) E	5 (15.6) 6	5 (16.1) 5	3 (10.0) 3	9 (28.1) 14
Dizziness	n (%) E	1 (3.1) 1	0	0	1 (3.1) 1
Headache	n (%) E	0	1 (3.2) 1	0	1 (3.1) 1
Investigations	n (%) E	0	0	4 (13.3) 7	4 (12.5) 7
White blood cells urine positive	n (%) E	0	0	1 (3.3) 2	1 (3.1) 2
Blood uric acid increased	n (%) E	0	0	1 (3.3) 1	1 (3.1) 1
Blood urine present	n (%) E	0	0	1 (3.3) 1	1 (3.1) 1
Haemoglobin decreased	n (%) E	0	0	1 (3.3) 1	1 (3.1) 1
Protein urine present	n (%) E	0	0	1 (3.3) 1	1 (3.1) 1
Red blood cells urine	n (%) E	0	0	1 (3.3) 1	1 (3.1) 1

MedDRA® System Organ Class MedDRA® Preferred Term	Statistic	Riluzole 50 mg Oral Soluble Film Fasting Conditions (N=32)	RILUTEK® 50 mg Tablet Fasting Conditions (N=31)	Riluzole 50 mg Oral Soluble Film Fed Conditions (N=30)	Overall (N=32)
Respiratory, thoracic and mediastinal disorders	n (%) E	1 (3.1) 1	1 (3.2) 1	0	2 (6.3) 2
Dysphonia	n (%) E	0	1 (3.2) 1	0	1 (3.1) 1
Pharyngeal hypoaesthesia	n (%) E	1 (3.1) 1	0	0	1 (3.1) 1
Psychiatric disorders	n (%) E	0	1 (3.2) 1	0	1 (3.1) 1
Insomnia	n (%) E	0	1 (3.2) 1	0	1 (3.1) 1
Skin and subcutaneous tissue disorders	n (%) E	1 (3.1) 1	0	0	1 (3.1) 1
Dry skin	n (%) E	1 (3.1) 1	0	0	1 (3.1) 1

E: Number of treatment-emergent adverse event; N: Number of Subjects Dosed; n (%): Number and percent of subjects with treatment-emergent adverse event; MedDRA®: Medical Dictionary for Regulatory Activities Version 19.1.
 Each subject could only contribute once to each of the incidence rates, regardless of the number of occurrences.
 Overall: Included results from all treatment groups.
 Data source: Listing 16.2.7-2

6.3.4. Laboratory Findings

There were no clinically significant shifts in any clinical chemistry or hematology parameters in any of the clinical studies. There were no Hy's Law cases.

6.3.5. Vital Signs

No relevant differences in mean values and changes from baseline were observed for vital signs.

6.3.6. **Swallowing Study 17M01R-0012**

Swallowing study 17M01R-0012 was a single site, single dose, open-label safety study in nine individuals with ALS.

The following evaluations were included.

- ALS Functional Rating Scale–Revised (ALSFRS-R).
- Videofluoroscopic Swallowing Study (VFSS)
- Episodes of penetration or aspiration quantified using the Penetration Aspiration Scale (PAS).

The primary endpoint was the change in PAS Score on VFSS before and after a single dose of 50 mg ROF. A PAS score of 1 or 2 indicates a safe swallow, 3-5 indicates penetration, and 6-8 indicates aspiration. The following table, copied from the submission, describes the PAS.

Table 3: Penetration Aspiration Scale (PAS). VF = Vocal Folds

Airway Safety Group	PAS Score	Definition
SAFE	1	Material does not enter airway.
	2	Material enters the airway, remains above VF, and is ejected from airway.
UNSAFE	3	Material enters the airway, remains above VF and is not ejected from airway.
	4	Material enters the airway, contacts VF and is ejected from airway.
	5	Material enters the airway, contacts VF and is not ejected from airway.
	6	Material enters the airway, passes below VF and is ejected into the larynx or out of airway.
	7	Material enters the airway, passes below VF and is not ejected from airway despite effort.
	8	Material enters the airway, passes below VF and no effort is made to eject.

Safe

Penetration

Aspiration



Analysis across each swallowing trial was performed, providing 12 bolus stimuli trials and approximately 35 swallows and PAS scores for each elicited swallow across testing within each participant.

Five (56%) patients were able to swallow safely by PAS standards both pre- and post-dose. One patient moved from the “safe” to “penetration” category. No patient had a score indicative of

Clinical Review

Rainer W. Paine, MD, PhD

NDA 212640

Exservan (Riluzole Oral Film)

aspiration either pre- or post-dose. Seven patients (78%) had the same summed score pre- and post- dose, while 2 patients (22%) improved their score. There were no patients whose sum of scores was worse following dosing.

6.4. Safety in the Postmarket Setting

6.4.1. Safety Concerns Identified Through Postmarket Experience

Based on the Periodic Safety Update (PSUR) for Rilutek® between 12/17/17 and 11/12/18, no new safety concern or risk was identified except for two cases of acute pancreatitis. Published literature review also identified a journal article describing two cases of acute pancreatitis associated with riluzole use (de Campos & de Carvalho, 2017). Pancreatitis was identified in the original riluzole clinical studies as an infrequent adverse event, occurring in 1/100 to 1/1000 patients. Pancreatitis is not mentioned in the current riluzole label. (b) (4), (b) (5)



6.5. Integrated Assessment of Safety

Oral hypoesthesia occurred in both the fasting and fed riluzole oral film groups (38% and 10%, respectively) but not with Rilutek tablets in the pivotal study 162020. There was no evidence that oral hypoesthesia adversely affected swallowing safety. There are no other new safety findings for riluzole except for two cases of acute pancreatitis reported in the postmarket setting which will be further investigated for potential inclusion in a future label revision.

7. Labeling Recommendations

7.1. Drug Labeling

This reviewer recommends adding additional information to Section 6 of the label about the rate of oral hypoesthesia observed with ROF (38%) compared to no patients with Rilutek in the pivotal study 162020.

8. Appendices

8.1. References

de Campos, C., & de Carvalho, M. (2017)
Riluzole-induced recurrent pancreatitis
Journal of Clinical Neuroscience 45: 153–154

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