CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212640Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	November 4, 2019
From	Teresa Buracchio, MD Eric Bastings, MD
Subject	Summary Memorandum
NDA/BLA # **Supplement#**	212640
Applicant	Aquestive Therapeutics
Date of Submission	1/31/2019
PDUFA Goal Date	11/30/2019
Proprietary Name / Non-Proprietary Name	Exservan (riluzole)
Dosage form(s) / Strength(s)	Oral film, 50 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of amyotrophic lateral sclerosis (ALS)
Regulatory Action	Approval

1. Background

The applicant has submitted a New Drug Application (NDA) for Exservan (riluzole) 50-mg oral film. The applicant is seeking approval through the 505(b)(2) regulatory pathway and is relying on the findings of safety and effectiveness for the listed drug (LD), Rilutek (riluzole 50-mg oral tablet), and on data from a relative bioavailability study for establishing a pharmacokinetic (PK) bridge between Exservan and the LD.

Riluzole 50-mg oral tablet was approved for "the treatment of patients with amyotrophic lateral sclerosis (ALS)" on December 12, 1995 (NDA 020599). The applicant proposes the same indication as Rilutek. The recommended dosage for riluzole is 50 mg taken orally twice daily. The oral film formulation of riluzole will provide an equivalent dose of the 50-mg tablet.

Riluzole oral film was granted orphan drug designation by FDA on January 23, 2018.

2. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

According to the OPQ review, the drug substance is produced with adequate quality to support approval of the NDA.

The drug 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). There are no novel excipients, and maximum daily exposures for excipients are within levels for FDA-approved products.

Stability and release testing were found to be acceptable. The stability data provides adequate support for a shelf-life of 24 months, when stored at controlled room temperature (68°–77° F). OPQ determined that the manufacturing process for the drug product is satisfactory. All manufacturing facilities for this product were found to be acceptable. There were no outstanding issues identified in the OPQ review.

OPQ recommends approval.

3. Nonclinical Pharmacology/Toxicology

There was no nonclinical information in the submission.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Gopichand Gottipati, with Dr. Sreedharan Sabarinath as Team Leader.

Study 162020, the pivotal bioequivalence study, was a single-center, open-label, single-dose, randomized, 5-period, crossover, comparative bioavailability study. Healthy subjects were randomized to receive a single dose of study medication or the reference formulation (under fasting or fed conditions) according to the randomization scheme. The study enrolled 45 subjects, and 30 subjects completed all treatment periods.

Bioavailability/Bioequivalence Assessment

The following table from the clinical study report for Study 162020 provides a summary of the comparative bioavailability data from the bioequivalence studies. Reference A refers to riluzole oral film and Reference B refers to riluzole tablets, both under fasting conditions.

Parameter	CV_{WR}	Geometric LSM (A)	Geometric LSM (B)	Ratio[1]	90% Geometric C.I.[2]		95% upper confidence bound[2]
					Lower	Upper	
AUC_{0-t} (ng*h/mL)	12.65%	780.01	714.48	109.17%	105.67%	112.79%	-
AUC_{0-inf} (ng*h/mL)	12.49%	795.98	730.02	109.04%	105.58%	112.61%	-
C_{max} (ng/mL)	32.66%	-	-	115.82%	-	-	-0.0123

[1] Point estimate of the geometric mean ratio (A/B).
[2] Reference-scaled average bioequivalence approach.
LSM: Least-squares mean

Source: Clinical study report (162020) Table 11.4.2.3-4, Page 71

The results show that the geometric means for AUC0-t, AUC0-inf, and for Cmax were approximately 109%, 109%, and 116%, respectively. OCP notes that this indicates a similar extent and rate of riluzole absorption after a single dose of the test and reference products under fasting conditions, which meets bioequivalence criteria.

Food Effects

The LD, riluzole tablet, has significant food effects. As described in the prescribing information for the LD, the Cmax decreases by approximately 45% and the AUC decreases by approximately 20% when administered with a high fat meal. The prescribing information (PI) for the listed drug specifies that riluzole should be administered “at least 1 hour before or 2 hours after a meal”.

Following the administration of riluzole oral film to healthy subjects under fed conditions with a high-fat meal, Cmax decreased by approximately 45%, and AUC decreased by about 15%. The food effects were comparable to the LD; therefore, OCP recommends that the dosing instructions for riluzole oral film should remain the same as for the LD.

OCP Recommendation:
OCP recommends approval based on the bioequivalence demonstrated between riluzole oral film and the LD.

5. Clinical- Efficacy

The effectiveness of riluzole oral film is based on the demonstration of bioequivalence to the LD.

6. Clinical- Safety

The safety of Exservan is based on the demonstration of bioequivalence to the LD. Dr. Rainer Paine, the clinical reviewer for this application, reviewed the new safety data in this submission. The safety review focused on the clinical studies conducted with riluzole oral film; however, Dr. Paine also reviewed safety data from the published literature and post-marketing safety reports for riluzole.

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

There were no deaths, serious adverse events, or discontinuations in the clinical development program.

A new safety signal of oral hypoesthesia was identified for the oral film formulation of riluzole. In the pivotal study (162020), oral hypoesthesia occurred in both the fasting and fed riluzole oral film groups (38% and 10%, respectively), compared with no occurrences in subjects taking riluzole tablets. The hypoesthesia was transient and resolved during the study. Circumoral paresthesia is described in the label for the LD. The rates of hypoesthesia observed with the riluzole oral film may potentially be related to greater contact with the oral mucosa than with the tablet formulation. All other adverse events were generally consistent with the established safety profile of riluzole.

A swallowing study, 17MO1R-0012, was a single-site, single-dose, open-label safety study in nine individuals with ALS. The study was terminated early due to enrollment challenges, and an interim analysis of 9 patients showed no evidence of swallowing dysfunction on videofluoroscopy.

In a review of the postmarketing safety data for Rilutek from 12/17/17 to 11/12/18, Dr. Paine identified two cases of acute pancreatitis. Additionally, a published literature review also

identified a journal article describing two cases of acute pancreatitis associated with riluzole use (de Campos & de Carvalho, 2017[1]). 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) (5) .

Clinical recommendation: Dr. Paine identified oral hypoesthesia as a new safety signal observed with this oral film formulation of riluzole. This will be described in Section 6 of the PI. Dr. Paine recommends approval of this supplement and I agree with his recommendation. A newly identified potential safety signal for pancreatitis will be further assessed under the originator product.

7. Advisory Committee Meeting

None required as drug is not a new molecular entity.

8. Pediatrics

The submission did not include any pediatric data. Because the product has orphan drug designation, Pediatric Research Equity Act (PREA) requirements were not triggered.

9. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

The Division of Medication Error and Prevention Analysis (DMEPA) and the Office of Prescription Drug Promotion (OPDP) provided consultations on the product labeling, including the proposed instructions for use (IFU).

10. Recommendations/Risk-Benefit Assessment

As the applicant has provided an adequate bridge to Rilutek, the findings of safety and efficacy of Rilutek, along with the new safety information provided by the applicant, support the approval of Exservan (riluzole oral film)

[1] de Campos, C., & de Carvalho, M. Riluzole-induced recurrent pancreatitis J Clin Neurosci. 201;45:153-154.

Oral hypoesthesia was identified as a new safety signal observed with this oral suspension formulation of riluzole in the pivotal bioequivalence study and will be described in labeling. This new safety finding does not impact the risk-benefit assessment of riluzole. A potential safety signal of pancreatitis was identified in a review of the postmarketing safety reports for riluzole and in a review of the published literature. (b) (5) .

Specific postmarketing risk management activities are not needed.

I agree with the review team that this NDA should be approved.

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/

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11/20/2019 10:43:13 AM

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11/22/2019 02:29:39 PM