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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

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Office of Clinical Pharmacology Review

NDA Number	212640
Link to EDR	\\CDSESUB1\evsprod\NDA212640\0001
Submission Date	1/31/2019
Submission Type	Original NDA – 505 (b)(2)
Product Name	Exservan® (Riluzole)
Dosage Form and Strength	Oral soluble film, 50 mg
Proposed Dose/Regimen	50 mg twice daily To be taken at least 1 hour before or 2 hours after a meal
Proposed Indication	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Applicant	Aquestive Therapeutics
OCP Division	Division of Clinical Pharmacology I
Associated IND	130939
OCP Review Team	Gopichand Gottipati Ph.D., Sreedharan Sabarinath Ph.D.

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1. Executive Summary

Aquestive Therapeutics submitted an original New Drug Application (NDA 212640) for EXSERVAN® for the treatment of Amyotrophic Lateral Sclerosis (ALS) via 505(b)(2) regulatory pathway. The proposed product is 50 mg oral soluble film. The listed drug is riluzole oral tablet (RILUTEK®) approved in the US in 1996.

This application relies on a pivotal relative bioavailability and food effect study (162020) conducted in healthy subjects to demonstrate a pharmacokinetic (PK) bridge between the proposed product (EXSERVAN® oral soluble film 50 mg) and the listed drug (RILUTEK® oral tablet 50 mg). In this single-dose study, the proposed product was administered without water and listed drug was administered with water, both under fasting conditions. The exposure metrics AUC and Cmax met bioequivalence criteria, therefore EXSERVAN® is bioequivalent to RILUTEK®. RILUTEK® has a food effect (administration of high fat meal decreased AUC by 20% and Cmax by 45% respectively), and therefore, it is required to administer RILUTEK® at least one hour before or two hours after a meal[1]. EXSERVAN® also had similar food effect. Administration of high-fat meal with EXSERVAN® decreased AUC by 15% and Cmax by 45% respectively. Therefore, EXSERVAN® should also be administered one hour before or two hours after a meal, like the listed drug. The relative bioavailability and food effect study conducted by the applicant provides an adequate scientific bridge for this 505(b)(2) application. Therefore, EXSERVAN® can rely on RILUTEK® and borrow information from its approved label.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study 162020. OSIS conducted inspection for the clinical site and found the data are reliable to support a regulatory decision (DARRTS 10/04/2019) and analytical site was previously inspected (DARRTS 04/29/2019). The NDA also included a pilot phase 1 PK study (1897) evaluating BA/BE and organoleptic effect.

2. Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval based on the bioequivalence demonstrated between 50 mg EXSERVAN® oral soluble film and listed drug RILUTEK® oral tablet 50 mg.

Since EXSERVAN® has food effects similar to that with the listed drug, EXSERVAN® should be taken at least one hour before or two hours after a meal, similar to the listed drug.

[1] USPI of Rilutek 50 mg tablets: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020599s017lbl.pdf

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3. Background and Regulatory History

The applicant is seeking approval for EXSERVAN® via 505(b)(2) pathway and are relying on FDA's findings of safety and efficacy of riluzole in addition to the results from the pivotal PK bridging study.

The original clinical development plan (summarized in Table 1 & Table 2) included two phase 1 studies: one pilot BA/BE organoleptic study (1897), and one pivotal relative bioavailability and food effect study (162020); and two phase 2 studies in subjects with ALS: swallowing study 17MO1R-0012 and the long Term (LT) safety study 17MO1R-0016.

In the pre-NDA meeting (dated March 2018), the adequacy of revised clinical development plan and overall submission package for EXSERVAN® was discussed. Upon review of adverse events reported in clinical study report for 162020, apart from oral hypoesthesia and erythema, the agency noted that no other concerning findings of oral cavity irritation were found. Therefore, the agency waived the conduct of study 17MO1R-0016 to assess chronic oral cavity irritation. The swallowing study 17MO1R-0012 was terminated early based on agreement with the agency.

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