CLINICAL UPDATE

Brand Name	Exservan™
Generic Name	riluzole
Drug Manufacturer	Aquestive Therapeutics

Clinical Update

TYPE OF CLINICAL UPDATE

New Brand and Dosage Form (oral film)

FDA APPROVAL DATE

November 22, 2019

LAUNCH DATE

May 10, 2021

REVIEW DESIGNATION

Standard; Orphan; New Drug Application (NDA): 212640

TYPE OF REVIEW

Type 3 - New Dosage Form

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

For the treatment of amyotrophic lateral sclerosis (ALS).

MECHANISMS OF ACTION

The mechanism by which riluzole exerts its therapeutic effects in patients with ALS is unknown. Riluzole modulates the actions of glutamate. The mechanism by which this happens is not clearly known but may include direct effects on the neurotransmitter itself and target receptors, the inhibition of glutamate release, blockade or inactivation of voltage-dependent sodium channels that are important for glutamate release, interference with intracellular events that result from binding of glutamate to receptors, and/or inhibition of arachidonic acid metabolism. Animal studies have shown that riluzole has a neuroprotective effect that delays neuronal injury or death.

DOSAGE FORM(S) AND STRENGTH(S)

Oral Film: 50 mg

DOSE & ADMINISTRATION

- Recommended dosage: 50 mg twice daily, taken at least 1 hour before or 2 hours after a meal.
- Measure serum aminotransferases before and during treatment.

EFFICACY

CLINICAL UPDATE

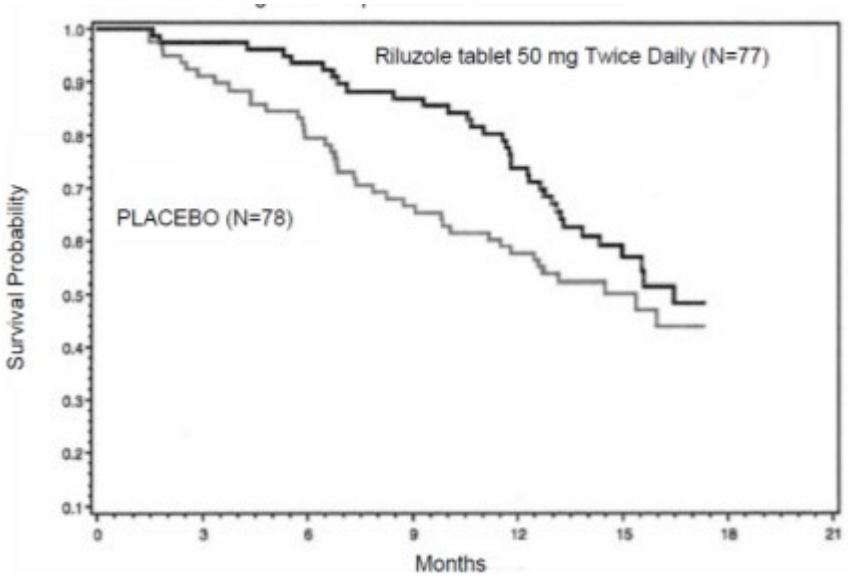
The efficacy of Exservan™ is based upon a relative bioavailability and food-effect study in healthy subjects comparing oral riluzole tablets to Exservan™ oral film.

The efficacy of riluzole was demonstrated in two studies (Study 1 and 2) that evaluated riluzole tablets 50 mg twice daily in patients with amyotrophic lateral sclerosis (ALS). Both studies included patients with either familial or sporadic ALS, a disease duration of less than 5 years, and a baseline forced vital capacity greater than or equal to 60% of normal.

Study 1 was a randomized, double-blind, placebo-controlled clinical study that enrolled 155 patients with ALS. Patients were randomized to receive riluzole tablets 50 mg twice daily (n=77) or placebo (n=78) and were followed for at least 13 months (up to a maximum duration of 18 months). The clinical outcome measure was time to tracheostomy or death.

The time to tracheostomy or death was longer for patients receiving riluzole tablets compared to placebo. There was an early increase in survival in patients receiving riluzole tablets compared to placebo. Figure 1 displays the survival curves for time to death or tracheostomy. The vertical axis represents the proportion of individuals alive without tracheostomy at various times following treatment initiation (horizontal axis). Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test p=0.12), the difference was found to be significant by another appropriate analysis (Wilcoxon test p=0.05). As seen in Figure 1, the study showed an early increase in survival in patients given riluzole tablets. Among the patients in whom the endpoint of tracheostomy or death was reached during the study, the difference in median survival between the riluzole tablets 50 mg twice daily and placebo groups was approximately 90 days.

Figure 1: Time to Tracheostomy or Death in ALS Patients in Study 1 (Kaplan-Meier Curves)



Study 2 was a randomized, double-blind, placebo-controlled clinical study that enrolled 959 patients with ALS. Patients were randomized to riluzole tablets 50 mg twice daily (n=236) or placebo (n=242) and were followed for at least 12 months (up to a maximum duration of 18 months). The clinical outcome measure was time to tracheostomy or death.

The time to tracheostomy or death was longer for patients receiving riluzole tablets compared to placebo. Figure 2 displays the survival curves for time to death or tracheostomy for patients randomized to either riluzole tablets 100 mg per day or placebo. Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test p=0.076), the difference was found to be significant by another appropriate analysis (Wilcoxon test p=0.05). Not displayed in Figure 2 are the results of

riluzole tablets 50 mg per day (one-half of the recommended daily dose), which could not be statistically distinguished from placebo, or the results of riluzole tablets 200 mg per day (two times the recommended daily dose), which were not distinguishable from the 100 mg per day results. Among the patients in whom the endpoint of tracheostomy or death was reached during the study, the difference in median survival between riluzole tablets and placebo was approximately 60 days.

Although riluzole tablets improved survival in both studies, measures of muscle strength and neurological function did not show a benefit.

Figure 2: Time to Tracheostomy or Death in ALS Patients in Study 2 (Kaplan-Meier Curves)