HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXSERVAN™ safely and effectively. See full prescribing information for EXSERVAN.

EXSERVAN (riluzole) oral film
Initial U.S. Approval: 1995

----------INDICATIONS AND USAGE----------

EXSERVAN is indicated for the treatment of amyotrophic lateral sclerosis (ALS) (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage: 50 mg twice daily, taken at least 1 hour before or 2 hours after a meal (2.1)
- Measure serum aminotransferases before and during treatment (2.2, 5.1)

----------DOSAGE FORMS AND STRENGTHS----------

Oral Film: 50 mg (3)

----------CONTRAINDICATIONS----------

Patients with a history of severe hypersensitivity reactions to riluzole or to any of its components (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatic injury: Use of EXSERVAN is not recommended in patients with baseline elevations of serum aminotransferases greater than 5 times upper limit of normal; discontinue EXSERVAN if there is evidence of liver dysfunction (5.1)
- Neutropenia: Advise patients to report any febrile illness (5.2)
- Interstitial lung disease: Discontinue EXSERVAN if interstitial lung disease develops (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence greater than or equal to 5% and greater than placebo) were oral hypoesthesia, asthenia, nausea, decreased lung function, hypertension, and abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aquestive Therapeutics at 1-877-394-5045 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Strong to moderate CYP1A2 inhibitors: Coadministration may increase EXSERVAN-associated adverse reactions (7.1)
- Strong to moderate CYP1A2 inducers: Coadministration may result in decreased efficacy (7.2)
- Hepatotoxic drugs: EXSERVAN-treated patients that take other hepatotoxic drugs may be at increased risk for hepatotoxicity (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXSERVAN is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

The recommended dosage for EXSERVAN is 50 mg taken orally twice daily. EXSERVAN should be taken at least 1 hour before or 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.

2.2 Monitoring to Assess Safety

Measure serum aminotransferases before and during treatment with EXSERVAN *[see Warnings and Precautions (5.1)]*.

2.3 Important Administration Instructions

Instruct patients and/or caregivers to read the "Instruction for Use" carefully for complete directions on how to properly dose and administer EXSERVAN oral films.

Apply EXSERVAN on top of the tongue where it adheres and dissolves. Do not cut or split the film.

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.

Only one oral film should be taken at a time.

3 DOSAGE FORMS AND STRENGTHS

Oral film: 50 mg orange, rectangular-shaped, orally dissolving film with "R50" printed in white on one side.

4 CONTRAINDICATIONS

EXSERVAN is contraindicated in patients with a history of severe hypersensitivity reactions to riluzole or to any of its components (anaphylaxis has occurred) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

EXSERVAN can cause liver injury. Cases of drug-induced liver injury, some of which were fatal, have been reported in patients taking riluzole. Asymptomatic elevations of hepatic transaminases have also been reported, and in some patients have recurred upon rechallenge with riluzole.

In clinical studies, the incidence of elevations in hepatic transaminases was greater in riluzole-treated patients than in placebo-treated patients. The incidence of elevations of ALT above 5 times the upper limit of normal (ULN) was 2% in riluzole-treated patients. Maximum increases in ALT occurred within 3 months after starting riluzole. About 50% and 8% of riluzole-treated patients in pooled controlled efficacy studies (Studies 1 and 2) had at least one elevated ALT level above ULN and above 3 times ULN, respectively *[see Clinical Studies (14)]*.

develop hepatic transaminases levels greater than 5 times the ULN. Discontinue EXSERVAN if there is evidence of liver dysfunction (e.g., elevated bilirubin). Concomitant use with other hepatotoxic drugs may increase the risk for hepatotoxicity *[see Drug Interactions (7.3)]*.

5.2 Neutropenia

EXSERVAN can cause neutropenia. Cases of severe neutropenia (absolute neutrophil count less than 500 per mm^3) within the first 2 months of riluzole treatment have been reported. Advise patients to report febrile illnesses.

5.3 Interstitial Lung Disease

EXSERVAN can cause interstitial lung disease, including hypersensitivity pneumonitis. Discontinue EXSERVAN immediately if interstitial lung disease develops.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described below and elsewhere in the labeling:

- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Controlled Clinical Trials of Riluzole Tablets

In the placebo-controlled clinical trials in patients with ALS (Study 1 and 2), a total of 313 patients received riluzole tablets 50 mg twice daily *[see Clinical Studies (14)]*. The most common adverse reactions in the riluzole-treated patients (in at least 5% of patients and more frequently than on placebo) were asthenia, nausea, decreased lung function, hypertension, and abdominal pain. The most common adverse reactions leading to discontinuation in the riluzole-treated patients were nausea, abdominal pain, constipation, and elevated ALT.

There was no difference in rates of adverse reactions leading to discontinuation in females and males. However, the incidence of dizziness was higher in females (11%) than in males (4%). The adverse reaction profile was similar in older and younger patients. There were insufficient data to determine if there were differences in the adverse reaction profile in different races.

Table 1 lists adverse reactions that occurred in at least 2% of riluzole treated patients (50 mg twice daily) in pooled Study 1 and 2, and at a higher rate than placebo.

Table 1. Adverse Reactions in Pooled Placebo-Controlled Trials (Studies 1 and 2) in Patients with ALS

	RILUZOLE Tablets 50 mg twice daily (N=313)	**Placebo (N=320)**

Asthenia	19	12
Nausea	16	11
Decreased lung function	10	9
Hypertension	5	4
Abdominal pain	5	4
Vomiting	4	2
Arthralgia	4	3
Dizziness	4	3
Dry mouth	4	3
Insomnia	4	3
Pruritus	4	3
Tachycardia	3	1
Flatulence	3	2
Increased cough	3	2
Peripheral edema	3	2
Urinary tract infection	3	2
Circumoral paresthesia	2	0
Somnolence	2	1
Vertigo	2	1
Eczema	2	1

Additional Adverse Reaction with EXSERVAN

In an open-label pharmacokinetic study in healthy subjects (n=32), oral hypoesthesia was observed in 38% of subjects taking EXSERVAN, compared to no subjects taking riluzole tablets, under fasting conditions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of riluzole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Acute hepatitis and icteric toxic hepatitis *[see Warnings and Precautions (5.1)]*
- Renal tubular impairment
- Pancreatitis

7 DRUG INTERACTIONS

7.1 Agents that may Increase Riluzole Blood Concentrations

CYP1A2 Inhibitors

Co-administration of EXSERVAN (a CYP1A substrate) with CYP1A2 inhibitors was not evaluated in a clinical trial; however, *in vitro* findings suggest an increase in riluzole exposure is likely.

The concomitant use of strong or moderate CYP1A2 inhibitors (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, oral contraceptives, thiabendazole, vemurafenib,

7.2 Agents that may Decrease Riluzole Plasma Concentrations

CYP1A2 Inducers

Co-administration of EXSERVAN (a CYP1A substrate) with CYP1A2 inducers was not evaluated in a clinical trial; however, *in vitro* findings suggest a decrease in riluzole exposure is likely. Lower exposures may result in decreased efficacy *[see Clinical Pharmacology (12.3)]*.

7.3 Hepatotoxic Drugs

Clinical trials in ALS patients excluded patients on concomitant medications which were potentially hepatotoxic (e.g., allopurinol, methyldopa, sulfasalazine). EXSERVAN-treated patients who take other hepatotoxic drugs may be at an increased risk for hepatotoxicity *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies of riluzole in pregnant women, and case reports have been inadequate to inform the drug-associated risk. The background risk for major birth defects and miscarriage in patients with amyotrophic lateral sclerosis is unknown. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In studies in which riluzole was administered orally to pregnant animals, developmental toxicity (decreased embryofetal/offspring viability, growth, and functional development) was observed at clinically relevant doses *[see Data]*. Based on these results, women should be advised of a possible risk to the fetus associated with use of EXSERVAN during pregnancy.

Data

Animal Data

Oral administration of riluzole (3, 9, or 27 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal growth (body weight and length) at the high dose. The mid dose, a no-effect dose for embryofetal developmental toxicity, is approximately equal to the recommended human daily dose (RHDD, 100 mg) on a mg/m^2 basis. When riluzole was administered orally (3, 10, or 60 mg/kg/day) to pregnant rabbits during the period of organogenesis, embryofetal mortality was increased at the high dose and fetal body weight was decreased and morphological variations increased at all but the lowest dose tested. The no-effect dose (3 mg/kg/day) for embryofetal developmental toxicity is less than the RHDD on a mg/m^2 basis. Maternal toxicity was observed at the highest dose tested in rat and rabbit.

When riluzole was orally administered (3, 8, or 15 mg/kg/day) to male and female rats prior to and during mating and to female rats throughout gestation and lactation, increased embryofetal mortality and decreased postnatal offspring viability, growth, and functional development were observed at the high dose. The mid dose, a no-effect dose for pre- and postnatal developmental toxicity, is approximately equal to the RHDD on a mg/m^2 basis.

8.2 Lactation

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