RILUTEK®

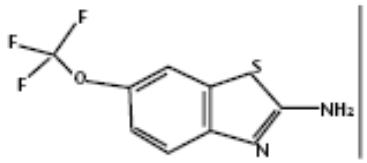
(RILUZOLE) TABLETS

RILUTEK®

(riluzole)Tablets
Rx only

DESCRIPTION

RILUTEK® (riluzole) is a member of the benzonthiazole class. Chemically riluzole is 2-amino-6-(trifluoromethoxy) benzonthiazole. Its molecular formula is $C_8H_5F_3N_2OS$ and its molecular weight is 234.2. Its structural formula is as follows:



Riluzole is a white to slightly yellow powder that is very soluble in dimethyformamide, dimethysolfuxide and methanol, freely soluble in dichloromethane, sparingly soluble in 0.1N HCl and very slightly soluble in water and 0.1N NaOH. RILUTEK is available as a capsule shaped, white, film coated tablet for oral administration containing 50mg of riluzole. Each tablet is engraved with "RPR 202" on one side.
Inactive Ingredients: Core : anhydrous dibasic calcium phosphate, USP; microcrystalline cellulose, NF; anhydrous colloidal silica, NF; magnesium stearate, NF; croscarmellose sodium, NF. **Film coating:** Hydroxypropyl methylcellulose, USP; polyethylene glycol 6000; titanium dioxide, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

The etiology and pathogenesis of amyotropic lateral sclerosis (ALS) are not known, although a number of hypotheses have been advanced. One hypothesis is that motor neurons, made vulnerable through either genetic predisposition or environmental factors, are injured by glutamate. In some cases of familial ALS, the enzyme superoxide dismutase has been found to be defective.
The mode of action of RILUTEK is unknown. Its pharmacological properties include the following, some of which may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.
Riluzole has also been shown, in a single study, to delay median time to death in a transgenic mouse model of ALS. These mice express human superoxide dismutase bearing one of the mutations found in one of the familial forms of human ALS.
It is also neuroprotective in various in vivo experimental models of neuronal injury involving excitotoxic mechanisms. In in vitro test, riluzole protected cultured rat motor neurons from the excitotoxic effects of glumatic acid and prevented the death of cortical neurons induced by anoxia. Due to its blockade of glutamatergic neurotransmission, riluzole also exhibits myorelaxant and sedative properties in animal models at doses of 30 mg/kg(about 20 times the recommended human daily dose) and anticonvulsant properties at a dose of 2.5 mg/kg (about 2 times the recommended human daily dose).

Pharmacokinetics

Riluzole is well-absorbed (approximately 90%), with average absolute oral bioavailability of about 60% (CV=30%). Pharmacokinetics are linear over a dose range of 25 to 100 mg given every 12 hours. A high fat meal decreases absorption, reducing AUC by about 20% and peak blood levels by about 45%. The mean elimination half-life of riluzole is 12 hours (CV=35%) after repeated doses. With multiple-dose administration, riluzole accumulates in plasma by about twofold and steady-state is reached in less than 5 days. Riluzole is 96% bound to plasma proteins, mainly to albumin and lipoproteins over the clinical concentration range. The 50 mg market tablet was equivalent, with respect to AUC, to the tablet used in the dose ranging clinical trials, while the

C_{max} was approximately 30% higher. Both tablets have been used in clinical trials. However if doses greater than those recommended are given, it is likely that higher plasma levels will be achieved, the safety of which has not been established (see DOSAGE AND ADMINISTRATION).

Metabolism and Elimination

Riluzole is extensively metabolized to six major and a number of minor metabolites, not all of which have been identified. Some metabolites appear pharmacologically active in in vitro assays. The metabolism of riluzole is mostly hepatic and consist of cytochrome P450-dependent hydroxylation and glucuronidation.

There is marked interindividual variability in the clearance of riluzole, probably attributable to variability of CYP1A2 activity, the principal isozyme involved in N-hydroxylation.

In vitro studies using liver microsomes show that hydroxylation of the primary amine group producing N-hydroxyriluzole is the main metabolic pathway in human, monkey, dog and rabbit. In humans cytochrome P450 1A2 is the principal isozyme involved in N-hydroxylation. In vitro studies predict that CYP 2D6, CYP 2C19, CYP 3A4 and CYP 2E1 are unlikely to contribute significantly to riluzole metabolism in humans. Whereas direct glucuroconjugation of riluzole (involving the glucurotransferase isoform UGT-HP4) is very slow in human liver microsomes, N-hydroxyriluzole is readily conjugated at the hydroxylamine group resulting in the formation of 0- (>90%) and N-glucuronides.

Following a single 150 mg dose of C-riluzole to 6 healthy males, 90% and 5% of the radioactivity was recovered in the urine and feces respectively over a period of 7 days.

Glucuronides accounted for more than 85% of the metabolites in urine. Only 2% of a riluzole dose was recovered in the urine as unchanged drug.

Special Populations

The pharmacokinetics of riluzole have not been studied in renally and hepatically impaired subjects, nor is there information about the effects of smoking, age and gender on the pharmacokinetics of riluzole but certain differences in the population subsets should be anticipated (see PRECAUTION).

Hepatic and Renal Disease: Since riluzole is extensively metabolized and subsequently excretred in the urine, it is likely that functional hepatic and renal impairment will reduce the clearance of riluzole and its metabolites and give higher plasma levels(see PRECAUTIONS and WARNINGS).

Age: Age-related decreased renal function would be expected to give higher plasma levels of riluzole and metabolites. However in controlled clinical trials, in which approximately 30% of patients were over 65, there were no differences in adverse events between younger and older patients (see PRECAUTIONS).

Gender: CYP 1A2 activity has been reported to be lower in women than in men. Therefore a gender effect on riluzole kinetics may be expected in women, resulting in higher blood concentration of riluzole and its metabolites (see PRECAUTIONS). No gender effect on favorable or adverse effects of riluzole was seen in controlled trials however.

Smoking: Cigarette smoking is known to induce CYP 1A2. Patients who smoke cigarettes would be expected to eliminate riluzole faster. There is no information, however, on the effect of, or need for dosage adjustment in these patients.

Race:

A clinical study conducted to evaluate the pharmacokinetics of riluzole and its metabolite Nhydroxyriluzole following repeated oral administration twice daily for 8 days in 16 healthy Japanese and 16 Caucasian adult males showed in the Japanese group a lower exposure of riluzole (C_{max} *0.85* [90% CI 0.68-1.08] and AUC inf. 0.88 [90% CI 0.69-1.13]) and similar exposure to the metabolite. The clinical significance of these results is not known.

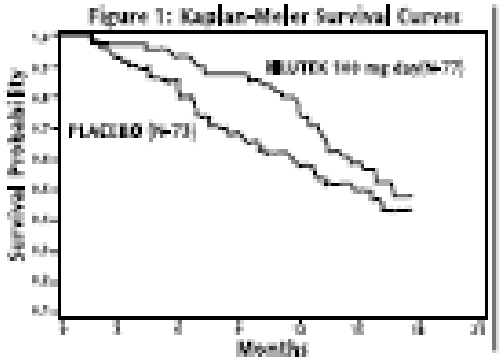
Clinical Trials

The efficacy of RILUTEK as a treatment of ALS was established in two adequate and well-controlled trials in which in which the time to tracheostomy or death was longer for patients randomized to RILUTEK than for those randomized to placebo.

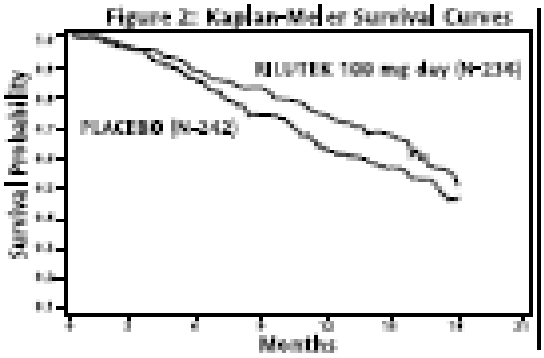
These studies admitted patients with either familial or sporadic ALS, a disease duration of less than 5 years, and a baseline forced vital capacity greater than or equal to 60%.

In one study, performed in France and Belgium, 155 ALS patients were followed for at least 13 months (maximum duration 18 months) after being randomized to either 100mg/day (given 50mg BID) of RILUTEK or placebo. Figure 1, which follows, displays the survival curves for time to death or tracheostomy. The vertical axis represents the proportion of individual alive without tracheostomy at various times following treatment initiation (horizontal axis). Although this

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, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in median survival of approximately 90 days. There was no statistically significant difference in mortality at the end of the study.



In the second study, performed in both Europe and North America, 959 ALS patients were followed for at least 1 year (North America centers) and up to 18 months (Europe centers) after being randomized to either 50,100, 200 mg/day of RILUTEK or placebo.
Figure 2, which follows displays the survival curves for time to death or tracheostomy for patients randomized to either 100 mg/day of RILUTEK or placebo. Although this 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 50 mg/day RILUTEK which could not be statistically distinguished from placebo and the results of 200mg/day which are essentially identical to 100mg/day. As seen, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in medial survival of approximately 60 days. there was no statistically significant difference in mortality at the end of the study



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

INDICATIONS AND USAGE
RILUTEK is indicated for the treatment of patients with Amyotropic Lateral Sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy.

CONTRAINDICATIONS
RILUTEK is contraindicated in patients who have history of severe hypersensitivity reactions to riluzole or any of the tablet components.

WARNINGS
Liver Injury / Monitoring Liver Chemistries

RILUTEK should be prescribed with care in patients with current evidence or history of abnormal liver function indicated by significant abnormalities in serum transaminase (ALT/SGPT;AST/SGOT), bilirubin, and / or gamma-glutamate transferace (GGT) levels (see PRECAUTIONS AND DOSAGE ADMINISTRATION sections). Baseline elevations of several LFTs (especially elevated bilirubin) should preclude the use of RILUTEK. RILUTEK, even in patients without a prior history of liver disease, causes serum aminotransferase elevations. Experience in almost 800 ALS patients indicates that about 50% of riluzole-treated patients will experience at least one ALT/SGPT level above the upper limit of normal, about 8% will have elevations > 3 X ULN, and about 2% of patients will have elevation > 5 ULN. A single non-ALS patient with epilepsy treated with concomitant carbamazepine and phenobarbital experienced marked, rapid elevations of liver enzymes with jaundice (ALT 26 X ULN, AST 17 X ULN, and bilirubin 11 x ULN) four months after starting RILUTEK; these returned to normal 7 weeks after treatment discontinuation.
Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when <5 times ULN. In trials, if ALT levels were <5 times ULN, treatment continued and ATL levels usually returned to below 2 times ULN within 2 to 6 months. Treatment in studies was discontinued, however, if ALT levels exceeded 5 X ULN, so that there is no experience with continued treatment of ALS patients once ALT values exceed 5 times ULN (see PRECAUTIONS: Laboratory Tests). There were instances of jaundice. Liver chemistries should be monitored (see PRECAUTIONS).

Neutropenia
Among approximately 400 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm³), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case was more complex, with marked anemia as well as neutropenia and the etiology of both is uncertain. Patients should be warned to report any febrile illness to their physicians. The report of febrile illness should prompt treating physicians to check white blood cell counts.

Interstitial lung disease
Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them were severe. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease (e.g. bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

PRECAUTIONS
Use in patients with Concomitant Disease
RILUTEK should be used with caution in patients with concomitant liver and/or renal insufficiency (see WARNINGS, CLINICAL PHARMCOLOGY). In particular, in cases of RILUTEK-induced hepatic injury manifested by elevated liver enzymes, the effect of the hepatic injury on RILUTEK metabolism is unknown.
Special Populations
Riluzole should be used with caution in elderly patients whose hepatic or renal functions maybe compromised due to age. Also, females may posses a lower metabolic capacity to eliminate riluzole compared to males respectively (see CLINICAL PHARMACOLOGY: Special Populations).

Information for the Patient
Patients should be advised to report any febrile illness to their physicians (see WARNINGS: Neutropenia).
Patients and caregivers should be advised that RILUTEK should be taken on a regular basis and at the same time of the day (e.g., in the morning and evening) each day. If a dose is missed, take the next tablet as originally planned (see DOSAGE AND ADMINISTRATION).
Patients should be warned about the potential for dizziness, vertigo, or somnolence and advised not to drive or operate machinery until they have gained sufficient experience on RILUTEK to gauge whether or not it affects their mental and/or motor performance adversely.
Whether alcohol increases the risk or serious hepatotoxicity with RILUTEK is unknown; therefore patients being treated with RILUTEK should be discouraged from drinking excessive amounts of

alcohol. Patients should also be made aware that RILUTEK should be stored at temperatures between 20ºC - 25ºC (68ºF – 77ºF) and protected from bright light.
RILUTEK must be kept out of reach of children.

Laboratory Tests
It is recommended that serum aminotransferases including ALT levels be measured before and during riluzole therapy. Serum ALT levels should be evaluated every month during the first 3 months of treatment, every 3 months during the remainder of the firs year, and periodically thereafter. Serum ALT levels should be evaluated more frequently in patients who develop elevations (see WARNINGS).
As noted in the WARNINGS Section, there is no experience with continued treatment of patients once ALT exceeds 5 X ULN. I f a decision is made to continue to treat these patients frequent monitoring (at least weekly) of complete liver function is recommended. Treatment should be discontinued if ALT exceeds10 X ULN or if clinical jaundice develops. Because there is no experience with rechallenge of patients who have had RILUTEK discontinued for ATL > 5 X ULN, no recommendations about restarting RILUTEK can be made.
In the two controlled trials in patients with ALS, the frequency with which values for hemoglobin, hematocrit, and erythrocyte counts fell below the lower limit of normal was greater in RILUTEK-treated patients than in placebo-treated patients; however these changes were mild and transient. The proportions of patients observed with abnormally low values for these parameters showed a dose-response relationship. Only one patient was discontinued from treatment because of severe anemia. The significance of this finding is unknown.

Drug Interactions
There have been no clinical studies designed to evaluate the interaction of riluzole with other drugs.
As with all drugs, the potential for interaction by a variety of mechanism is a possibility.
Hepatotoxic Drugs: The clinical trials in ALS excluded patients on concomitant medications which were potentially hepatotoxic (e.g., allopurinol, methyldopa, sulfasalazine). Accordingly, there is no information about the safety of administering RILUTEK in conjunction with such medications. If the practitioner chooses to prescribe such a combination, caution should be exercised.
Drugs Highly Bound To Plasma Proteins: Riluzole is highly bound (96%) to plasma proteins, binding mainly to serum albumin and to lipoproteins. The effect of riluzole (up to 5 mcg/mL) on warfarin (5mcg/mL) binding did not show any displacement of warfarin. Conversely, riluzole binding was unaffected by the addition of warfarin, digoxin, imipramine, and quinine at high therapeutic concentrations.
Effect of Other Drugs On Riluzole Matabolism: In vitro studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interaction may occur when riluzole is given concurrently with agents that affect CYP 1A2 activity. Potential Inhibitors of CYP 1A2 (e.g., caffeine, phenacetin, theophylline, amitriptyline, and quinolones) could decrease the rate of riluzole elimination, while inducers of CYP 1A2 (e.g., cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.
Effect of Riluzole on the Metabolism of Other Drugs: CYP 1A2 is the principal isoenzyme involved in the initial oxidative metabolismmof riluzole; potential interactions may occur when riluzole is given concurrently with other agents which are also metabolized primarily by CYP 1A2 (e.g., theophylline, caffeine, and tacrine). Currently it is not known whether riluzole has any potential for enzyme induction in humans.
Drug Laboratory Test Interactions: None known
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term studies to determine the carcinogenic potential of riluzole have not yet been completed. The genotoxic potential of riluzole was evaluated in the bacterial mutagenicity (Ames) test, the mouse lymphoma mutation assay in L5178Y cells, the in vitro chromosomal aberration assay in human lymphocytes and the in vivo rat cytogenetic assay and in vivo mouse micronucleus assay in bone marrow. There was no evidence of mutagenic or clastogenic potential in the Ames test, the mouse lymphoma assay, or the in vivo assays in the mouse and rat. There was no equivocal clastogenic response in the in vitro lymphocyte chromosomal aberration assay, which was not reproduced in a second assay performed at equal or higher concentrations; riluzole was therefore considered non-clastogenic in human lymphocytes.
N-hydroxyriluzole, the major active metabolite of riluzole, was found positive for the induction of chromosome damage in mouse lymphoma cells in vitro (mouse lymphoma assay and

micronucleus test in L5178Y cell line), but did not induce gene mutations in this cells (HPRT test in L5178Y cell line). Moreover since N-hydroxyriluzole was negative in all other in vitro tests (two Ames tests with and without rat or hamster S9, an in vitro UDS test on rat hepatocytes, two chromosome aberration test in human lymphocytes) and in an in vivo test (micronucleus test in mouse bone marrow), this clastogenic effect was considered not relevant in humans.
Riluzole impaired fertility when administered to male and female rats prior to and during mating at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m^2 basis (see PRECAUTIONS: “Pregnancy” for effects on fertility).

Pregnancy

Pregnancy category C:
Oral administration of riluzole to pregnant animals during the period of organogenesis caused embryotoxicity in rats and rabbits at doses of 27mg/kg and 60 mg/kg,respectively, or 2.6 and 11.5 times, respectively, the recommended maximum human daily dose on a mg/m^2 basis.
Evidence of maternal toxicity was also observed at these doses.
When administered to rats prior to and during mating (males and females) and throughout gestation and lactation (females), riluzole produced adverse effects on pregnancy (decreased implantations, increased intrauterine death) and offspring viability and growth at an oral dose 15 mg/kg or 1.5 times the maximum daily dose on a mg/m^2 basis.
There are no adequate and well controlled studies in pregnant women. Riluzole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

In rat studies, C riluzole was detected in maternal milk. It is not known whether riluzole is excreted in human breast milk. Because many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants from Rilutek is unknown, women should be advised not to breast-feed during the treatment with RILUTEK.

Use in the Elderly

Age-related compromised renal and hepatic function may cause a decrease in clearance of riluzole (see CLINICAL PHARMACOLOGY: Special Populations). In controlled clinical trials, about 30% of patients were over 65. There were no differences in adverse effects between younger and older patients.

Pediatric Use

The safety and effectiveness of RILUTEK in pediatric patients have not been established.

ADVERSE REACTIONS

The most common observed AEs associated with the use of RILUTEK more frequently than placebo treated patients were: asthenia, nausea, dizziness, decreased lung function, diarrhea, abdominal pain, pneumonia, vomiting, vertigo, circumoral paresthesia, anorexia, and somnolence. Asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia were dose related.
Approximately 14% (n=141) of the 982 individuals with ALS who received RILUTEK in pre-marketing clinical trials discontinued treatment because of an adverse experience. Of those patients who discontinued due to adverse events, the most commonly reported were: nausea, abdominal pain, constipation, and ALT elevations. In a dose response study in ALS patients, the rates of discontinuation of RILUTEK for asthenia, nausea, abdominal pain and ALT elevation were dose related.

Incidence in Controlled ALS Clinical Studies

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients with ALS treated with RILUTEK (n=794) participating in placebo-controlled trials and were numerically greater in the patients treated with RILUTEK 100mg/day than with placebo or for which a dose response relationship is suggested.
The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the AE incidences in the population studied.

Table 1
Adverse Events Occurring in Placebo-Controlled Clinical Trials
†Percentage of patients reporting events

Body System/ Adverse Event†	Riluzole 50 mg/day (N=237)	Riluzole 100 mg/day (N=313)	Riluzole 200 mg/day (N=244)	Placebo (N=320)
Body as a Whole				
Asthenia	14.8	19.2	20.1	12.2
Headache	8.0	7.3	7.0	6.6
Abdominal pain	6.8	5.1	7.8	3.8
Back pain	1.7	3.2	4.1	2.5
Aggravation reaction	0.4	1.3	2.0	0.9
Malaise	0.4	0.6	1.2	0.0
Digestive				
Nausea	12.2	16.3	20.5	10.6
Vomiting	4.2	4.2	4.5	1.6
Dyspepsia	2.5	3.8	6.1	5.0
Anorexia	3.8	3.2	8.6	3.8
Diarrhea	5.5	2.9	9.0	3.1
Flatulence	2.5	2.6	2.0	1.9
Stomatitis	0.8	1.0	1.2	0.0
Tooth disorder	0.0	1.0	1.2	0.3
Oral Moniliasis	0.4	0.6	1.2	0.3
Nervous				
Hypertonia	5.9	6.1	5.3	5.9
Depression	4.2	4.5	6.1	5.0
Dizziness	5.1	3.8	12.7	2.5
Dry mouth	3.0	3.5	2.0	3.4
Insomnia	2.1	3.5	2.9	3.4
Somnolence	0.8	1.9	4.1	1.3
Vertigo	2.5	1.9	4.5	0.9
Circumoral paresthesia	1.3	1.6	3.3	0.0
Skin and Appendages				
Pruritus	3.8	3.8	2.5	3.1
Eczema	0.8	1.6	1.6	0.6
Alopecia	0.0	1.0	1.2	0.6
Exfoliative dermatitis	0.0	0.6	1.2	0.0
Respiratory				
Decreased lung function	13.1	10.2	16.0	9.4
Rhinitis	8.9	6.4	7.8	6.3
Increased cough	2.1	2.6	3.7	1.6
Sinusitis	0.4	1.0	1.6	0.9
Cardiovascular				
Hypertension	6.8	5.1	3.3	4.1
Tachycardia	1.3	2.6	2.0	1.3
Phlebitis	0.4	1.0	0.8	0.3
Palpitation	0.4	0.6	1.2	0.9
Postural Hypotension	0.8	0.0	1.6	0.6
Metabolic and Nutritional Disorders				
Weight loss	4.6	4.8	3.7	4.7
Peripheral edema	4.2	2.9	3.3	2.2
Musculoskeletal System				
Arthralgia	5.1	3.5	1.6	3.4
Urogenital System				
Urinary tract infection	2.5	2.6	4.5	2.2
Dysuria	0.0	1.0	1.2	0.3

Other Adverse Events Observed

Other events which occurred in more than 2% of patients treated with RILUTEK.
100 mg/day but equally or more frequently in the placebo group included: accidental injury, apnea, bronchitis, constipation, death, dysphagia, dyspnea, flu syndrome, heart arrest, increased sputum, pneumonia, and respiratory disorder.
The overall adverse event profile for RILUTEK was similar between females and males, and was independent of age. Because the largest non-white racial subgroup was only 2% of patients exposed to RILUTEK (18/794) in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experience reports by race. In ALS studies, dizziness did occur more commonly in females (11%) than in males (4%). There was not a difference between females and males in the rates of discontinuation of RILUTEK for individual adverse experiences.

Other Adverse Events Observed During All Clinical Trials

RILUTEK has been administered to 1713 individuals during all clinical trials, some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology.
The frequencies presented represent the proportion of the 1713 individuals exposed to RILUTEK who experience an event on the type cited on at least one occasion while receiving RILUTEK.
All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.
***=AE frequency ≤ to placebo**

Body as a Whole: *Frequen*t: Hostility*. *Infrequent*: Abscess*, sepsis*, photosensitivity reaction*, cellulites, face edema*, hernia, peritonitis, attempted suicide, injection site reaction, chills*, flu syndrome, intentional injury, enlarged abdomen, neoplasm. *Rare:* Acrodynia, hypothermia, moniliasis*, rheumatoid arthritis.

Digestive System: *Infrequent*: Increased appetite, intestinal obstruction*, Fecal impaction, gastrointestinal hemorrhage, gastrointestinal ulceration gastritis*, fecal incontinence, jaundice, hepatitis, glossitis, gum hemorrhage*, pancreatitis, tenesmus, esophageal stenosis, *Rare*: Cheilitis*, cholecystitis, hematemesis, melena*, biliary pain, proctitis, pseudomembranous enterocolitis, enlarged salivary gland, tongue discoloration, tooth caries.

Nervous System: *Frequent*: Agitation*, tremor. *Infrequent*: Hallucinations, personality disorder*, abnormal thinking*, coma, paranoid reaction*, manic reaction, ataxia, extrapyramidal syndrome, hypokinesia, urinary retention, emotional liability, delusions, apathy, hypesthesia, incoordination, confusion*, convulsion, leg cramps, amnesia, dysarthria, increased libido, stupor, subdural hematoma, abnormal gait, delirium, depersonalization, facial paralysis, hemiplegia, decreased libido, myoclonus. *Rare:* Abnormal dreams, acute brain syndrome, CNS depression, dementia, cerebral embolism, euphoria*, hypotonia, ileus*, peripheral neuritis, psychosis*, psychotic depression, schizophrenic reaction, trimus, wristdrop.

Skin and Appendages: *Infrequent:* Skin ulceration, urticaria, psoriasis, seborrhoea*, skin disorder, fungal dermatitis*, *Rare:* Angiodema, contact dermatitis, erythema multiforme, furunculosis*, skin moniliasis, skin granuloma, skin nodule.

Respiratory System: *Infrequent:* Hiccup, pleural disorder*. Asthma, epistaxis, hemoptysis, yawn, *hyperventilation,* lung edema*,* hypoventilation*,* lung carcinoma*,* hypoxia, laryngitis, pleural effusion, pneumothorax*, respiratory moniliasis, stridor*.*

Respiratory, thoracic and mediastinal disorders
Uncommon: interstitial lung disease (see warnings)

Cardiovascular System: *Infrequent:* Syncope*, hypotension, heart failure, migraine, peripheral vascular disease, angina pectoris*, myocardial infarction*, ventricular extrasystoles, cerebral hemorrhage, atrial fibrillation*, bundle branch block, congestive heart failure, pericarditis, lower extremity embolus, myocardial ischemia*, shock*, *Rare:* bradycardia, cerebral ischemia, hemorrhage, mesenteric artery occlusion, subarachnoid hemorrhage, supraventricular tachycardia*, thrombosis, ventricular fibrillation, ventricular tachycardia.

Metabolic and Nutritional Disorders: *Infrequent:* Gout*, respiratory acidosis, edema, thirst*, hypokalemia, hyponatremia, weight gain*, *Rare:* Generalized edema, hypercalcemia, hypercholesteremia.

Endocrine System: *Infrequent:* Diabetes mellitus, thyroid neoplasia. *Rare:* Diabetes insipidus, parathyroid disorder.

Hemic and Lymphatic System: *Infrequent:* Anemia*, leukocytosis, leucopenia, ecchymosis, *Rare:* Neutropenia, aplastic anemia, cyanosis, hypochromic anemia, iron deficiency anemia, lymphadenopathy, petechiae*, purpura.

Musculoskeletal System: *Infrequent:* Arthosis, myasthenia*, bone neoplasm. *Rare:* Bone necrosis, osteoporosis, tetany.

Special Senses: *Infrequent:* Amblyopia, opthalmitis. *Rare:* Blepharitis, cataract, deafness, diplopia*, ear pain, glaucoma, hyperacusis, photophobia, taste loss, vestibular disorder.

Urogenital System: *Infrequent:* Urinary urgency, urine abnormality, urinary incontinence, kidney calculus, hematuria, impotence, prostate carcinoma, kidney pain, metrorrhagia, priapism.
Rare: Amenorrhea, breast abscess, breast pain, nephritis*, nocturia, pyelonephritis, enlarged uterine fibroids, uterine hemorrhage, vaginal moniliasis.

Laboratory Test: *Infrequent:* Increase gamma glutamyl transferase, abnormal liver functions/test, increased alkaline phhosphatase, positive direct Coombs test, increase gamma globulins.
Rare: Increased lactic dehydrogenase.

OVERDOSAGE
No specific antidote or information on treatment of overdose with RILUTEK is available. In the event of overdose, RILUTEK therapy should be discontinued immediately. Treatment should be supportive and directed towards alleviating symptoms.
Experience with riluzole overdose in humans is limited. Methemoglobinemia or undetermined origin has been reported in association with a riluzole overdose many times the recommended daily dose. This was rapidly reversible after treatment with methylene blue. The estimated oral median lethal dose is 94 mg/kg and 39 mg/kg for male mice and rats, respectively.

DOSAGE AND ADMINISTRATION
The recommended dose for RILUTEK is 50 mg every 12 hours. No increased benefit can be expected from higher daily doses, but adverse events are increased.
RILUTEK tablets should at least be taken an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability.
Special Populations
Patients with Impaired or Renal or Hepatic Function: Studies have not yet been completed in these populations (see WARNINGS, PRECAUTIONS, CLINICAL PHARMACOLOGY).

HOW SUPPLIED
RILUTEK 50 mg tablets are white, film coated, capsule-shaped and engraved with “RPR 202” on one side. RILUTEK is supplied in bottles of 60 tablets. NDC 0075-7700-60.

STORE AT CONTROLLED ROOM TEMPERATURE 20°C -25°C (68°F – 77°F) AND PROTECT FROM BRIGHT LIGHT.

KEEP OUT OF THE REACH OF CHILDREN.

MANUFACTURED BY:
Opella Healthcare International SAS
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REVISION DATE
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