Package Insert for RILUTEK® Tablets

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

RILUTEK® Tablets

COMPOSITION:

Each tablet contains: riluzole 50 mg

PHARMACOLOGICAL CLASSIFICATION:

A 34 - Other

PHARMACOLOGICAL ACTION:

The precise mechanism of action of riluzole is unknown but may relate to: 1) inhibition of glutamate release, 2) inactivation of voltage-dependent sodium channels, 3) non-competitive blockade of N-methyl-D-aspartic acid (NMDA) receptors and 4) stimulation of a G-protein dependent signal transduction pathway.

Pharmacokinetic Properties:

The pharmacokinetics of riluzole have been evaluated in healthy male volunteers after single oral administration of 25 to 300 mg and after multiple-dose oral administration of 25 to 100 mg twice a day. Plasma levels increase linearly with the dose and the pharmacokinetic profile is dose-dependent. Steady-state plasma levels are reached within 3 to 8 days.

Riluzole is rapidly absorbed after oral administration with maximal plasma concentrations occurring within 60 to 90 minutes. About 90 % of the dose is absorbed and the absolute bioavailability is 60 %. The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in Cmax of 44 %, decrease in AUC of 17 %).

Riluzole is extensively distributed throughout the body. The volume of distribution of riluzole is about 245 litres (3,4 l/kg). Riluzole is about 97 % protein bound and it binds mainly to serum albumin and to lipoproteins.

Unchanged riluzole is the main component in plasma and is extensively metabolised by cytochrome P450 and subsequent glucuronidation. *In vitro* studies using human liver preparations demonstrated that cytochrome P450 1A2 is the principal isoenzyme involved in the riluzole metabolism.

The primary metabolic pathway for riluzole is initial oxidation by cytochrome P450 1A2 producing N-hydroxy-riluzole, the major active metabolite of riluzole. This metabolite is rapidly

glucuronoconjugated to O- and N- glucuronides.
The elimination half-life ranges from 9 to 15 hours. Riluzole is eliminated mainly in the urine. The overall urinary excretion accounts for about 90 % of the dose; two thirds of which are glucuronide conjugates.

Special populations:

Race:

A clinical study was conducted to evaluate the pharmacokinetics of riluzole and its metabolite N-hydroxy-riluzole following repeated oral administration twice daily for 8 days in healthy Japanese and Caucasian adult males. There were no ethnic differences in pharmacokinetic parameters of riluzole and its metabolite between the Japanese and Caucasian subjects.

INDICATIONS:

RILUTEK is indicated for the extension of survival of patients with the bulbar variant of motor neuron disease.

CONTRA-INDICATIONS:

Patients who have a history of severe hypersensitivity reactions to riluzole or any of the tablet components.
Patients who have hepatic disease or who have baseline transaminases greater than 3 times the upper limit of normal.
Patients who are pregnant or lactating (See “Pregnancy and Lactation”).

WARNINGS:

Increased alanine-aminotransferase (ALT) usually appeared within 3 months after the start of therapy with RILUTEK; they were usually transient and levels returned to below 2 times the ULN after 2 to 6 months while treatment was continued. These increases could be associated with jaundice. In patients with increases in ALT to more than 5 times the ULN, treatment was discontinued and the levels returned to less than 2 times the ULN within 2 to 4 months.

Because of the risks of hepatitis, serum transaminases including ALT should be measured before and during therapy with RILUTEK. ALT should be measured every month during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter. ALT levels should be measured frequently in patients who developed elevated ALT levels.

RILUTEK should not be used in patients who have active hepatic disease.

Patients should be warned about the potential for dizziness, vertigo or somnolence, and advised not to drive or operate machinery if these symptoms occur.

INTERACTIONS:

There have been no clinical studies to evaluate the interactions of RILUTEK with other drugs. *In vitro* studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isoenzyme involved in the initial oxidative metabolism of RILUTEK. Inhibitors of CYP 1A2 (e.g. caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones) could potentially decrease the rate of RILUTEK elimination, while inducers of CYP 1A2 (e.g. cigarette smoke, charcoal-broiled food, rifampicin and omeprazole) could increase the rate of RILUTEK elimination.

PREGNANCY AND LACTATION:

RILUTEK is contra-indicated in pregnant and lactating patients, as safety has not been established.

DOSAGE AND DIRECTIONS FOR USE:

The recommended daily dose in adults is 100 mg (50 mg every 12 hours). RILUTEK should be taken between mealtimes i.e. at least one hour before or two hours after a meal.

No significant increased benefit can be expected from higher daily doses.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10 000 to < 1/1000); very rare (< 1/ 10 000); not known (cannot be estimated from the available data).

Gastrointestinal disorders:

Very common: Nausea

Common: Diarrhoea, abdominal pain, vomiting

Uncommon: Pancreatitis

Frequent: Anorexia

Less frequent: Colitis, stomatitis, peritonitis, rectal disorder, pseudomembranous enterocolitis, peptic ulcer haemorrhage, dyspepsia, flatulence, oral moniliasis

Nervous system disorder:

Common: Headache, dizziness, oral paraesthesia, somnolence

Frequent: Vertigo

Less frequent: Amnesia, coma, depression, hypertonia

General disorders and administration site conditions:

Very common: Asthenia

Common: Pain

Less frequent: Chest pain, back pain, malaise and headache

Skin and Appendages:

Less frequent: Eczema, nail disorder, pruritus, alopecia, exfoliative dermatitis

Cardiovascular:

Common: Tachycardia

Less frequent: Hypertension, arrhythmia, postural hypotension

Respiratory system:

Frequent: Decreased lung function, pneumonia

Musculoskeletal system:

Less frequent: Arthralgia

Urogenital system:

Less frequent: Urinary tract infection, dysuria

Blood and lymphatic system disorders:

Uncommon: Anaemia

Not known: Neutropenia

Metabolic and Nutritional:

Less frequent: Peripheral oedema, weight loss

Hepato-biliary disorders:

Very common: Abnormal liver function tests

Not known: Hepatitis

Immune system disorders:

Uncommon: Anaphylactoid reaction, angioedema

Laboratory tests:

Frequent: Increases in ALT, aspartate aminotransferase (AST) (see “Warnings” and “Special Precautions”). Increases in lactate dehydrogenase (LDH), gamma-glutamate transferase (GGT), bilirubin, alkaline phosphatase, creatine phosphokinase (CPK).

Special Precautions:

The safety and effectiveness in any neurodegenerative process occurring in children or adolescents has not been established.

RILUTEK should be used with caution in patients with renal insufficiency.

- **Liver impairment**:

RILUTEK should be prescribed with care in patients with a history of abnormal liver function, or in patients with slightly elevated serum transaminases (ALT; AST up to 3 times ULN), bilirubin and/or gamma-glutamyl transferase (GGT) levels. Baseline elevations of several liver function tests (especially elevated bilirubin) should preclude the use of RILUTEK.
RILUTEK should be discontinued if the ALT levels increase to five times the ULN.
There is no experience with dose reduction or re-challenge in patients who have developed an increase of ALT to 5 times ULN. Re-administration of RILUTEK to patients in this situation cannot be recommended.

- **Neutropenia**:

Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt physicians to check white blood cell counts and to discontinue RILUTEK in case of neutropenia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Refer to “Side Effects” for possible symptoms of overdosage.
Neurological and psychiatric symptoms, acute toxic encephalopathy with stupor, coma, and methemoglobinaemia have been observed.
No specific treatment information or antidote is available.
In case of overdosage, treatment is symptomatic and supportive.
Severe methemoglobinaemia may be rapidly reversible after treatment with methylene blue.

IDENTIFICATION:

RILUTEK is a white capsule-shaped film coated tablet containing 50 mg of riluzole. Each tablet is engraved with "RPR 202" on one side of the tablet.

PRESENTATION:

RILUTEK tablets are packaged in opaque PVC/Aluminium blister packs containing 56 tablets.

STORAGE INSTRUCTIONS:

RILUTEK tablets must be stored below 25 °C and protected from light. RILUTEK must be kept out of the reach of children.

REGISTRATION NUMBER:

30/34/0229

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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