PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

RILUTEK® 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg riluzole.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

4.3 Contraindications

- Hypersensitivity to riluzole or any of the excipients listed in section 6.1.
- Hepatic disease or baseline transaminases greater than 3 times the upper limit of normal.
- Patients who are pregnant or breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

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/SGPT; AST/SGPT up to 3 times the upper limit of the normal range (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 (see section 4.8).

Because of the risk of hepatitis, serum transaminases, including ALT, should be measured before and during therapy with riluzole. 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 more frequently in patients who develop elevated ALT levels.

RILUTEK should be discontinued if the ALT levels increase to five times the ULN. There is no experience with dose reduction or rechallenge 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 medical practitioners. The report of a febrile illness should prompt medical practitioners to check white blood cell counts and to discontinue RILUTEK in case of neutropenia (see section 4.8).

Interstitial lung disease

Cases of interstitial lung disease have been reported in patients treated with riluzole, as in RILUTEK, some of them were severe (see section 4.8). If respiratory symptoms develop such as

dry cough and/or dyspnoea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease (e.g. bilateral diffuse lung opacities), RILUTEK should be discontinued immediately. In the majority of the reported cases, symptoms resolved after discontinuation and symptomatic treatment.

Sodium

RILUTEK contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially “sodium free”.

4.5 Interaction with other medicines and other forms of interaction

There have been no clinical studies to evaluate the interactions of RILUTEK with other medicines. *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.

4.6 Fertility, pregnancy and lactation

Pregnancy

RILUTEK is contraindicated in pregnancy (see sections 4.3 and 5.3). Clinical experience with riluzole, as in RILUTEK, in pregnant women is lacking.

Breastfeeding

RILUTEK is contraindicated in breastfeeding women (see sections 4.3 and 5.3). It is not known whether riluzole is excreted in human milk.

Fertility

Fertility studies in rats revealed slight impairment of reproductive performance and fertility at doses of 15 mg/kg/day (which is higher than the therapeutic dose), probably due to sedation and lethargy.

4.7 Effects on ability to drive and use machines

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

No studies on the effects on the ability to drive a vehicle and use machines have been performed.

4.8 Undesirable 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).

Blood and lymphatic system disorders

Uncommon: Anaemia

Not known: Neutropenia (see section 4.4)

Immune system disorders

Uncommon: Anaphylactoid reaction, angioedema

Metabolism and nutrition disorders

Uncommon: Peripheral oedema, weight loss

Nervous system disorders

Common: Headache, dizziness, oral paraesthesia, somnolence, vertigo

Uncommon: Amnesia, coma, depression, hypertonia

Cardiac disorders

Common: Tachycardia

Uncommon: Hypertension, arrhythmia, postural hypotension

Respiratory, thoracic, and mediastinal disorders

Common: Decreased lung function, pneumonia

Gastrointestinal disorders

Very common: Nausea

Common: Diarrhoea, abdominal pain, vomiting, anorexia

Uncommon: Pancreatitis, colitis, stomatitis, peritonitis, rectal disorder, pseudomembranous *enterocolitis*, peptic ulcer haemorrhage, dyspepsia, flatulence, oral moniliasis

Hepato-biliary disorders

Very common: Abnormal liver function tests

Not known: Hepatitis

Skin and subcutaneous disorders

Uncommon: Eczema, nail disorder, pruritus, alopecia, exfoliative dermatitis

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia

Renal and urinary disorders

Uncommon: Urinary tract infection, dysuria

General disorders and administration site conditions

Very common: Asthenia

Common: Pain

Uncommon: Chest pain, back pain, malaise

Investigations

Common: Increases in ALT, aspartate aminotransferase (AST) (see section 4.4). Increases in lactate dehydrogenase (LDH), gamma-glutamate transferase (GGT), bilirubin, alkaline phosphatase, creatine phosphokinase (CPK).

Description of selected adverse reactions

Hepato-biliary disorders

Increased alanine aminotransferase usually appeared within 3 months after the start of therapy with riluzole; they were usually transient, and levels returned to below twice the ULN after 2 to 6 months while treatment was continued. These increases could be associated with jaundice. In patients (n = 20) from clinical studies 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 in most cases (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of RILUTEK is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Side effects can be reported directly to Sanofi's Pharmacovigilance Unit at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Symptoms

Refer to section 4.8 for possible symptoms of overdosage.

Neurological and psychiatric symptoms, acute toxic encephalopathy with stupor, coma, and methaemoglobinaemia have been observed.

Management

No specific treatment information or antidote is available. In case of overdosage, treatment is symptomatic and supportive. Severe methaemoglobinaemia may be rapidly reversible after treatment with methylene blue.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.11 Other medicines acting on the central nervous system

Pharmacotherapeutic group: other nervous system drugs

ATC code: N07XX02.

Mechanism of 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.

5.2 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.

Absorption

Riluzole is rapidly absorbed after oral administration with maximal plasma concentrations occurring within 60 to 90 minutes (C_{max} = 173 ± 72 (sd) ng/mL). About 90 % of the dose is absorbed and the absolute bioavailability is 60 ± 18 %.

The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in C_{max} of 44 %, decrease in AUC of 17 %).

Distribution

Riluzole is extensively distributed throughout the body and has been shown to cross the blood brain barrier. The volume of distribution of riluzole is about 245 ± 69 L (3,4 L/kg). Riluzole is about 97 % protein bound and it binds mainly to serum albumin and to lipoproteins.

Biotransformation

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.

Elimination

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

Linearity: 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.

Special populations

Impaired renal function

There is no significant difference in pharmacokinetic parameters between patients with moderate

or severe chronic renal insufficiency (creatinine clearance between 10 and 50 mL/min) and healthy volunteers after a single oral dose of 50 mg riluzole.

Older people

The pharmacokinetic parameters of riluzole after multiple dose administration (4,5 days of treatment at 50 mg riluzole bid) are not affected in the older people (> 70 years).

Impaired hepatic function

The AUC of riluzole after a single oral dose of 50 mg increases by about 1,7-fold in patients with mild chronic liver insufficiency and by about 3-fold in patients with moderate chronic liver insufficiency.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Dibasic calcium phosphate, anhydrous

Microcrystalline cellulose

Colloidal silica, anhydrous

Magnesium stearate

Croscarmellose sodium.

Coating:

Hypromellose

Macrogol 6000

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

Opaque PVC/Aluminium blister packs containing 56 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

Tel: 011 256 3700

8. REGISTRATION NUMBER

30/34/0229

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Registered: 07 October 1996.

10. DATE OF REVISION OF THE TEXT

10 March 2026.