AUSTRALIAN PRODUCT INFORMATION - TEGLUTIK® (riluzole)

1. NAME OF THE MEDICINE

Riluzole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of oral suspension contains 5 mg of riluzole.

Riluzole is a white to slightly yellow powder. It is very slightly soluble in water and 0.1N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid; and very soluble in methanol, acetone, acetonitrile, dichloromethane and dimethyl sulfoxide.

1 mL of oral suspension contains 400 mg of sorbitol (equivalent to 571.43 mg of sorbitol solution (70% w/w)). For the full list of excipients, see Section 6 List of excipients.

3. PHARMACEUTICAL FORM

TEGLUTIK® is an oral suspension containing riluzole, a benzothiazole. Chemical name: 6-(trifluoromethoxy)-2-benzothiazolamine It is a slightly brown, opaque homogenous suspension after manually shaken.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Riluzole is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS).

4.2 DOSAGE AND ADMINISTRATION

Dosage

The recommended dose is 10 mL (equivalent to 50 mg riluzole) two times a day. The maximum recommended daily dose is 100 mg (50 mg every 12 hours). No significant increase in benefit can be expected from higher daily doses.

Due to the reduction in absorption observed when administered with high fat meals, riluzole should not be taken with a fat containing meal.

Method of administration

The suspension can be given per oral administration. Dilution with liquids is not necessary.

The suspension is administered by means of graduated dosing syringe orally or via a Percutaneous Endoscopic Gastrostomy (PEG).

The suspension must be manually gently shaken for at least 30 seconds by rotating the bottle by 180° and the homogeneity should be visually verified.

Open the bottle, connect the dosing syringe to the bottle syringe-adapter, invert the bottle and, by maintaining the bottle in the inverted position, slowly withdraw the suspension volume corresponding to the recommended dose (i.e. 10 mL corresponds to 50 mg of Riluzole).

After the administration of the suspension, thoroughly wash the syringe with tap water. The PEG tube should be washed with tap water before and after administration of the suspension.

Paediatric

The safety and effectiveness of riluzole in any neurodegenerative diseases occurring in children or adolescents have not been established.

Renal impairment

See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

Hepatic impairment

See **Section 4.3 CONTRAINDICATIONS** and **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.**

4.3 CONTRAINDICATIONS

Patients who have a history of severe hypersensitivity reactions to riluzole or any of the excipients.

Patients who have a hepatic disease or hepatic impairment (baseline transaminases greater than 3 times the upper limit of normal).

Patients who are pregnant or lactating.

This product contains sorbitol.
Patients with rare hereditary problems of fructose intolerance should not take this medicine (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment

Riluzole is contraindicated in patients with hepatic disease or hepatic impairment (baseline transaminases greater than 3 times the upper limit of normal).

Riluzole should be prescribed with care in patients with a history of abnormal liver function, or in patients with slightly elevated serum transaminase (ALT/SGPT; AST/SGOT up to 3 times the ULN), bilirubin and/or gamma-glutamyl transferase (GGT) levels. Baseline elevations of several liver function tests (especially elevated bilirubin) should preclude the use of riluzole.

Elevations of alanine-aminotransferase (ALT) levels to more than 3 times the upper limit of the normal range (ULN) were observed in about 10 % of the patients treated with riluzole compared to 3.7 % in the placebo group; levels increased to more than 5 times the ULN in about 3% of the patients treated with riluzole compared to 2% of the placebo treated patients. The increases in ALT usually appeared within 3 months after the start of therapy with riluzole; they were usually transient and levels returned to below 2 times the ULN after 2 to 6 months while treatment was continued. These increases were rarely 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 risks 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.

Riluzole 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. Readministration of riluzole to patients in this situation cannot be recommended.

Use in renal impairment

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

Hereditary fructose intolerance

The product contains liquid sorbitol (E420) therefore patients with rare hereditary problems of fructose intolerance should not take this medicine.

Neutropenia

There have been three reports (3/5000) of marked neutropenia where absolute neutrophil count was less than 500/mm^3. Refer to Adverse Events section. 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 riluzole in case of neutropenia.

Interstitial lung disease

Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them were severe (see Adverse Effects section). 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 reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

Use in elderly

See **Section 5.2 PHARMACOKINETICS PROPERTIES**.

Paediatric use

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There have been no clinical studies to evaluate the drug interactions of riluzole with other drugs. Experiments on mice and rats indicated that riluzole potentiated the hypnotic effects of hexobarbitone and chlorpromazine.

The metabolism of riluzole is mostly hepatic and consists of cytochrome P450-dependent hydroxylation and glucuronidation. There is marked inter-individual variability in the clearance of riluzole, probably attributable to variability of CYP 1A2 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 humans. 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 CYP2E1 are unlikely to contribute significantly to riluzole metabolism in humans.

Effect of riluzole on the metabolism of other drugs: Potential interactions may occur when riluzole is given concurrently with other agents which are also metabolized primarily by CYP 1A2 (eg, theophylline, caffeine and tacrine). It is not known whether riluzole has any potential for enzyme induction in humans.

Effect of other drugs on riluzole metabolism: Potential interactions may occur when riluzole is given concurrently with other agents that affect CYP 1A2 activity. Potential inhibitors of CYP 1A2 (eg. caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones) could decrease the rate of riluzole elimination, while inducers of CYP 1A2 (eg. cigarette smoke, charcoal-broiled food, rifampicin and omeprazole) could increase the rate of riluzole elimination.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effect of fertility

Riluzole impaired fertility when administered to male and female rats prior to mating and during mating at an oral dose of 15 mg/kg (approximately 13 times human exposure at the maximum recommended clinical dose of 100mg, based on AUC).

Use in Pregnancy (Category B3)

In the pregnant rat, the transfer of ^{14}C- riluzole across the placenta to the foetus has been detected. There was no evidence of embryotoxicity or teratogenicity in the offspring of rats or rabbits following maternal treatment with riluzole during organogenesis at oral doses of up to 27 and 60 mg/kg/day respectively, corresponding to plasma exposures (based on AUC) 61 and 18 times higher than those anticipated in clinical use. However, foetal growth and

development were slightly retarded, possibly as a consequence of maternal toxicity. Foetal growth was not affected following maternal exposure to riluzole at levels approximately 6 to 8-fold higher (based on AUC) than those anticipated in clinical use.

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) and offspring viability and growth at an oral dose of 15mg/kg (approximately 13 times human exposure at the maximum recommended clinical dose of 100mg, based on AUC).

There are no adequate and well-controlled studies in pregnant women. Riluzole must not be used in pregnant women.

Use in Lactation

^{14}C-riluzole and/or its metabolites were detected in the milk of lactating rats at levels 2.5-fold higher than those appearing in maternal plasma. There was an increased incidence of postnatal mortality in the offspring of rats treated with riluzole during the peri-natal period at oral doses of 15 mg/kg/day, which represents exposure (on the basis of AUC) to levels 13-fold higher than those anticipated in clinical use. It is not known whether riluzole is excreted in human milk; therefore, women should not breast-feed during treatment with riluzole.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

In Phase III studies conducted in North America and Europe, the most frequent side effects related to riluzole were asthenia, nausea, and elevations in liver function tests. The following table includes all the adverse events that occurred at a frequency of 1% or more among ALS patients receiving riluzole 100mg/day:

Adverse Events Occurring in Placebo-Controlled Clinical Trials Percentage of patients reporting events			
Adverse Event		***Riluzole 100mg/day (N=395)***	***Placebo (N=406)***
Cardiac Disorders	Heart Arrest	3.0	2.7
	Tachycardia	3.0	1.5
	Peripheral Oedema	2.5	1.7
Ear and Labyrinth Disorders	Vertigo	1.8	1.0

Gastrointestinal Disorders	Dysphagia	15.4	18.2
	Nausea	14.2	9.1
	Constipation	8.1	9.4
	Abdominal Pain	5.1	3.7
	Diarrhoea	3.5	3.2
	Dyspepsia	3.3	4.2
	Dry Mouth	3.0	3.2
	Vomiting	3.0	1.2
	Flatulence	1.8	1.0
General Disorders and Administration Site Conditions	Death	27.3	33.3
	Asthenia	17.5	11.6
	Pain	4.8	2.0
	Flu Syndrome	3.0	4.2
	Chest Pain	1.0	1.5
	Neck Pain	1.0	1.0
Infections and Infestations	Bronchitis	12.9	14.5
	Pneumonia	3.3	3.2
	Urinary Tract Infection	3.3	2.7
	Concurrent Infection	1.5	0.7
	Pharyngitis	1.3	2.2
	Infection	1.0	1.7
Injury and Poisoning	Accidental Injury	7.8	9.6
Investigations	Weight Loss	3.8	3.7
	Hepatic function abnormal / Increased ALT	11.1	1.0
	Increased AST	1.3	0.5
Metabolism and Nutrition Disorders	Anorexia	2.8	3.0
Musculoskeletal, Connective Tissue and Bone Disorders	Back Pain	3.0	2.2
	Arthralgia	2.5	2.5
	Stiffness/Spasticity (Joint Disorder)	2.0	0.7
	Myalgia	1.0	1.5
Nervous System Disorders	Headache	6.6	5.4
	Hypertonia	5.3	6.2
	Dizziness	2.8	2.0
	Insomnia	2.8	3.7
	Somnolence	2.0	1.0
	Circumoral Parasthesia	1.3	0.0
Psychiatric Disorders	Depression	4.1	4.4
	Aggravation Reaction	1.3	1.2
	Nervousness	1.3	1.2
	Anxiety	1.0	1.0
Renal and Urinary Disorders	Urinary Frequency	1.0	0.7

Respiratory, Thoracic and Mediastinal Disorders	Respiratory Disorder	13.4	15.8
	Lung Function Decrease	12.7	14.5
	Apnoea	8.1	9.4
	Rhinitis	5.8	4.7
	Dyspnoea	5.3	5.7
	Lung Disorder	2.3	3.0
	Sputum Increase	2.3	4.9
	Cough Increased	1.8	1.2
	Pulmonary Embolus	1.3	1.2
	Aspiration Pneumonia	1.0	0.5
Skin and Subcutaneous Tissue Disorders	Pruritus	3.0	3.2
	Eczema	1.3	0.5
	Sweating	1.0	2.0
Vascular Disorders	Hypertension	5.1	4.4

The adverse events reported in the comparative bioavailability study between TEGLUTIK® oral suspension and riluzole tablets are reported by body system in the table here below:

Body system	**Test – N = 30**		**Reference – N = 30**	
Preferred term	**N AES**	**N (%) Subjects**	**N AEs**	**N (%) Subjects**
All body system	13	9 (30.0)	11	5 (16.7)
Nervous system disorders	6	6 (20.0)	4	4 (13.3)
Headache	3	3 (10.0)	3	3 (10.0)
Dizziness	1	1 (3.3)	1	1 (3.3)
Presyncope	2	2 (6.7)	0	0 (0.0)
Gastrointestinal disorders	5	4 (13.3)	7	4 (13.3)
Vomiting	1	1 (3.3)	4	4 (13.3)
Nausea	1	1 (3.3)	2	2 (6.7)
Paraesthesia oral	2	2 (6.7)	0	0 (0.0)
Dry mouth	1	1 (3.3)	0	0 (0.0)
Dyspepsia	0	0 (0.0)	1	1 (3.3)
Musculoskeletal and connective tissue disorders	1	1 (3.30	0	0 (0.0)
Neck pain	1	1 (3.3)	0	0 (0.0)
Reproductive system and breast disorders	1	1 (3.3)	0	0 (0.0)
Dysmenorrhoea	1	1 (3.3)	0	0 (0.0)

Note:
Test= TEGLUTIK®
Reference: riluzole tablets

A slightly higher risk of the adverse events considered related to Cmax (ie ~20% higher than riluzole tablets) of TEGLUTIK® oral suspension (e.g. dizziness, diarrhoea, asthenia and ALT increase) cannot be excluded.

The following is a list of adverse reactions reported from clinical trials and post marketing studies with an incidence of less than 1%:

Uncommon 0.1 – 1 %
Rare 0.01 – 0.1%
Very Rare <0.01%
Not Known (cannot be estimated from the available data)

Cardiac Disorders
Rare: angina unstable, atrial fibrillation, cardiac failure.
Very Rare: arrhythmia.

Gastrointestinal Disorders
Uncommon: pancreatitis
Rare: gastrointestinal disorder, gastric ulcer, gastrointestinal haemorrhage, gastrointestinal irritation, melaena.

General Disorders And Administration Site Conditions
Rare: condition aggravated, malaise, weakness, pyrexia.
Very Rare: anaphylactoid reaction.

Hepato-Biliary Disorders
Rare: hepatitis, jaundice, hepatocellular damage.

Immune System Disorders
Uncommon: anaphylactoid reaction, angioedema
Rare: hypersensitivity.

Laboratory Investigations
Rare: gamma-glutamyltransferase increased, liver function tests abnormal, transaminase increased, blood bilirubin increased, blood alkaline phosphatase increased, haematocrit decreased, blood creatine phosphokinase increased, glycosuria present, haemoglobin decreased, leukocyte count decreased, platelet count decreased.

Metabolism And Nutrition Disorders
Rare: dehydration.
Very Rare: hyponatraemia.

Nervous System Disorders
Very Rare: amnesia.

Psychiatric Disorders
Rare: motor dysfunction, paraesthesia nec, completed suicide, confusion, delirium, hallucination, personality change due to a general medical condition.

Respiratory, Thoracic And Mediastinal Disorders
Uncommon: respiratory failure (exc neonatal), interstitial lung disease (see Precautions section).

Rare: asphyxia, respiratory distress.

Skin & Subcutaneous Tissue Disorders
Rare: dermatitis
Very Rare: angioedema.

Blood and Lymphatic System Disorders
Uncommon: anaemia
Rare: erythropenia, leucopoenia, thrombocytopenia.
Very Rare: neutropenia - among approximately 5000 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 associated with marked anaemia and the aetiology is uncertain.

4.9 OVERDOSE

Neurological and psychiatric symptoms, acute toxic encephalopathy with stupor, coma and methemoglobinaemia have been observed in isolated cases. Severe methemoglobinaemia may be rapidly reversible after treatment with methylene blue. In case of overdose, treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The aetiology and pathogenesis of amyotrophic lateral sclerosis (ALS) are not known, although a number of hypotheses have been advanced. One hypothesis is that motor neurones made vulnerable through either genetic predisposition or environmental factors, are injured by glutamate. In some cases of familial ALS, enzyme superoxide dismutase has been found to be defective.

The mechanism of action of riluzole has not been completely elucidated but evidence to date suggests that it may involve inactivation of voltage dependent sodium channels and impairment of glutamatergic neurotransmission.

There are no validated animal models of ALS in which to test riluzole. Riluzole has been shown to cross the blood brain barrier and to possess neuroprotective properties in various *in vivo* experimental models of neuronal injury known to involve excitotoxic mechanisms, such as cerebral ischemia. *In vitro*, riluzole protects cultured rat motorneurones from the excitotoxic effects of glutamic acid and prevents the death of cortical neurones induced by anoxia. In healthy volunteers at therapeutic doses, riluzole has been shown to protect to some extent against the hypobaric hypoxia induced at an equivalent altitude of 5000

m. Also, riluzole moderately reduces the cerebral metabolic rate of glucose as shown by PET-scan.

Due to its blockade of glutamatergic neurotransmission, riluzole also has myorelaxant and sedative properties in animal studies at doses of 30 mg/kg (about 20 times the human recommended daily dose) and anticonvulsant properties at doses of 2.5 mg/kg (about 2 times the human recommended daily dose).

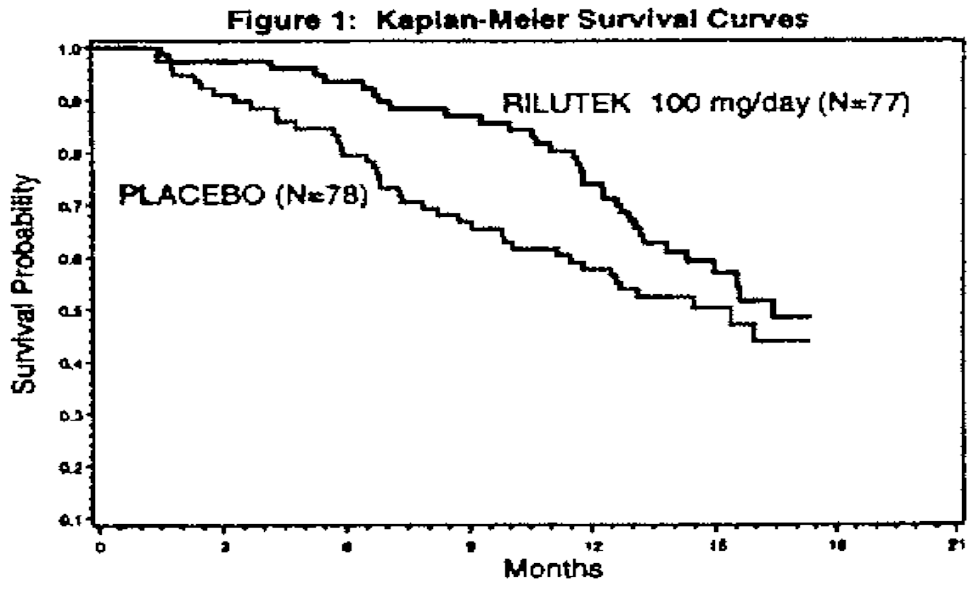
Clinical Trials

Two multinational, multicenter, double-blind, parallel group trials have demonstrated that TEGLUTIK® extends survival for patients with ALS regardless of the onset type. It is also concluded that the survival benefit is maintained.

In a first trial, 155 patients were randomised to riluzole 100 mg/day (50 mg twice daily) or placebo and were followed-up for 12 to 21 months. While there was no change from baseline in the functional evaluation, survival was significantly prolonged for patients who received riluzole as compared to patients who received placebo. The median survival time was 17.7 months versus 14.9 months for riluzole and placebo respectively.

Riviere et al. (1998) analysed extended survival in ALS patients treated with riluzole in this study. Post hoc analysis suggested that the patients receiving riluzole remained in the milder health states longer ($p<0.05$, Cox model). Patients with advanced disease were less responsive.

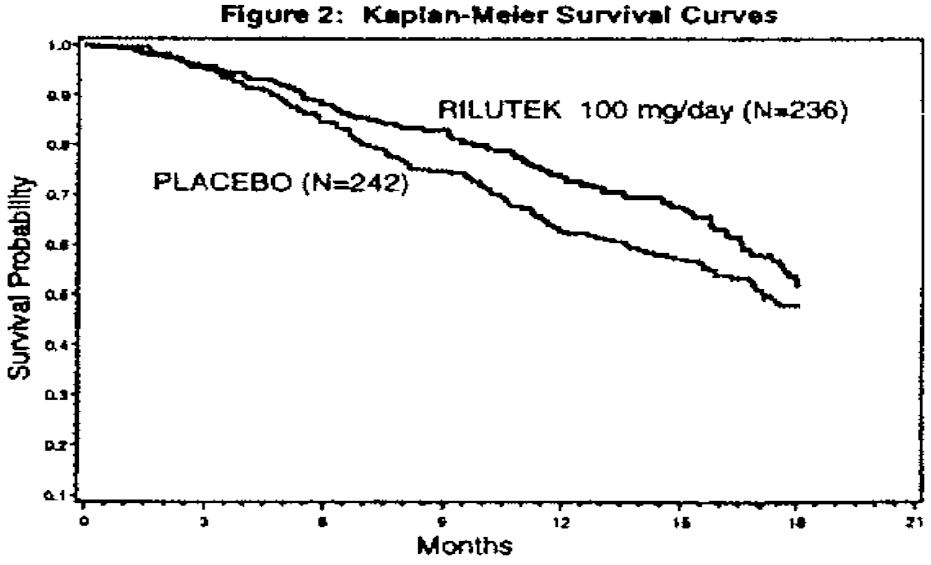
Figure 1: Kaplan Meier survival curve for 100mg riluzole vs placebo.



In a second dose-ranging trial, 959 patients with ALS were randomised to one of four treatment groups: riluzole 50, 100, 200 mg/day, or placebo and were followed-up for 18 months. In patients treated with riluzole 100 mg/day, survival was significantly longer compared to patients who received placebo. The median

survival time approached 16.5 months versus 13.5 months for riluzole 100mg/day and placebo, respectively. There were no changes from baseline observed in the functional evaluation. The effect of 50 mg/day was not statistically significant compared to placebo and the effect of 200 mg/day was essentially comparable to that of 100 mg/day.

Figure 2: Kaplan Meier survival curve for 100mg riluzole vs. placebo. with 95% confidence interval.



A separate compassionate-use study (n=168), enabling access to treatment for patients excluded from the two pivotal studies, was designed to assess the efficacy and safety of riluzole in patients at a late stage of the disease. In this population with decreased respiratory function (baseline vital capacity less than 60%), survival time and motor function in the riluzole group did not differ significantly from that of placebo. It was anticipated that up to 300 patients would enter this study, but only 168 were enrolled (86 received placebo, 82 received riluzole). Thus the statistical power of the study was diminished.

In a double-blind placebo-controlled trial designed to assess the efficacy and safety of riluzole in Japanese patients, patients were randomised to riluzole 100mg/day (50mg twice daily) or placebo and were followed-up for 18 months. In this study, the efficacy was assessed on inability to walk alone, loss of upper limb function, tracheostomy, need for artificial ventilation, gastric tube feeding or death. Tracheostomy-free survival in patients treated with riluzole did not differ significantly from placebo. Due to the low incidence of ALS in Japan, and for practical reasons, the study was limited to 100 patients per treatment group. The small size of this study resulted in a lack of statistical power to detect a significant difference between riluzole and placebo.

Meta analysis, including this study and those described above, showed a less striking effect of survival for riluzole as compared to placebo although the differences remained statistically significant.

A Cochrane Review of data from the two pivotal studies (first trial and dose ranging trial) found that there was a significant difference in percent mortality at 12 months between riluzole 100mg/day and placebo groups. Results were expressed as odds ratios (OR) and 95% CI for continuous variables. With regards to the primary outcome (mortality at 12 months) the OR for the combined studies was 0.57 (95% CI 0.41 to 0.80, p=0.001). There was no evidence of heterogeneity (Chi- square, p= 0.58). Overall there was a 23% reduction in risk of death in those patients receiving riluzole (p=0.0509).

A United Kingdom National Institute for Clinical Excellence (NICE) Review of the clinical effectiveness of riluzole found that it was effective in the treatment of ALS. In a meta-analysis which included data from the two pivotal studies and the compassionate study, it was found that for tracheostomy-free survival over 18 months the hazard ratio was 0.83 (95% CI 0.69-0.99). The report concluded that there was evidence of a modest benefit for patients taking riluzole.

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 bid. Plasma levels increase linearly with the dose and the pharmacokinetic profile is dose-independent. Steady-state plasma levels are reached within 3 to 8 days.

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%. With multiple dose administration (10 day treatment at 50mg riluzole bid), unchanged riluzole accumulates in plasma by about 2 fold and steady-state is reached in less than 5 days.

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%).

In a comparative bioavailability study the AUC_0-α of riluzole 50 mg tablets and of TEGLUTIK® (riluzole) 50 mg/10 mL oral suspension were equivalent. (Ratio: 106.46%; 90% CI: 96.68 - 117.23%). Riluzole is more rapidly absorbed after the administration of oral suspension (Tmax approximately 30 minutes) with a mean Cmax approximately 20% higher than after the administration of riluzole tablets (Ratio: 122.32%; 90% CI: 103.28-144.88%) (See **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

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 ± 69L (3.4 L/kg). Riluzole is about 97% protein bound and it binds mainly to serum albumin and to lipoproteins.

Metabolism

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 consists of cytochrome P450-dependent hydroxylation and glucuronidation.

There is marked interindividual variability in the clearance of riluzole, probably attributable to variability of CYP 1A2 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 O- (>90%) 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.

Special populations

Elderly: The pharmacokinetics of riluzole in elderly subjects were compared to young healthy subjects and no clinically significant differences were found.

Gender: No gender effect on the pharmacokinetics of riluzole was found, however CYP 1A2 activity has been reported to be lower in women than in men and thus a higher blood concentration of riluzole and its metabolites is possible in women.

A comparative bioavailability study has been conducted between TEGLUTIK® oral suspension and riluzole tablets. The results showed, as reported also in the literature, a higher exposure in female subjects in terms of Cmax (~25%) and AUC

(~53%) of TEGLUTIK® oral suspension compared to male subjects. However, no relevant clinical impact is expected.

Smoking: Cigarette smoking is known to induce CYP 1A2 and thus it is possible that patients who smoke may eliminate riluzole faster. There is no information available on the effect or need for dosage adjustment.

Race: Clearance of riluzole in native Japanese subjects was found to be 50% lower compared to Caucasian subjects (after normalizing for body weight). Although it is not clear if this difference is due to genetic or environmental factors (eg. smoking, alcohol, coffee and dietary preferences) it is possible that Japanese subjects may possess a lower capacity (oxidative and/or conjugative) for metabolising riluzole. There are no studies, however, of lower doses in Japanese subjects.

Paediatrc: the safety and efficacy of riluzole in children has not been studied.

Renal impairment: Study results showed that the pharmacokinetic profile of a single dose of riluzole is similar between patients with moderate or severe chronic renal insufficiency (creatinine clearance between 10 and 50 mL/min) and healthy subjects. A multiple dose study in renally impaired patients has not been performed.

Hepatic impairment: The AUC of riluzole after a single oral dose of 50mg 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. Refer to Contraindications and Precautions sections.

5.3 PRECLINICAL SAFETY

Carcinogenicity

Two long term (2 years) carcinogenicity studies have been completed in rats and mice. Riluzole showed no evidence of carcinogenic potential in rats and mice treated orally for 2 years at doses of 10 and 20 mg/kg/day, respectively. These doses were approximately 0.85 times the recommended maximum dose of 100mg daily, on a mg/m^2 basis.

There was no evidence of a genotoxic potential in standard assays for gene mutations (microbial mutagenicity test, mouse lymphoma assay in L5178Y cells) and chromosomal damage (chromosomal aberrations in human lymphocytes *in vitro*, rat cytogenetic assay *in vivo* and mouse micronucleus assay).

6. PHYSICOCHEMICAL PROPERTIES

6.1 LIST OF EXCIPIENTS

The oral suspension also contains sorbitol solution (70% w/w) (non-crystallising), aluminium magnesium silicate, xanthan gum, saccharin sodium, antifoam AF emulsion Q7-2587, sodium lauryl sulfate, ceteareth-25, and purified water.

6.2 INCOMPATIBILTIES

See 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

TEGLUTIK® oral suspension has a shelf life of 3 years when stored below 25°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

After the first opening: 15 days, without any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

1 mL of oral suspension contains 5 mg of riluzole.
The suspension is supplied in an amber glass bottle equipped with a LDPE syringe-adapter and closed by means of a white-white HDPE child-proof screw cap.

Pack sizes of one or two bottles of 250 mL of TEGLUTIK® 5 mg/mL Oral Suspension.

Pack size of one bottle of 300 mL of TEGLUTIK® 5 mg/mL Oral Suspension.

The bottle is packed with a plastic graduated oral dosing syringe. The syringe barrel is graduated in millilitres up to 10 mL.

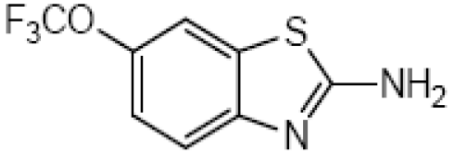
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



CAS 1744-22-5

7. MEDICINE SCHEDULE (POISIONS STANDARD)

Schedule 4 (S4): Prescription Only Medicine

8. SPONSOR

Seqirus Pty Ltd ABN: 26 160 735 035
63 Poplar Road
Parkville VIC 3052

9. DATE OF FIRST APPROVAL

21 August 2018

10. DATE OF REVISION

[To be completed at the time of any approval of a variation to the approved PI.]

Summary table of changes

Section Changed	Summary of new information

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