SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TEGLUTIK 5 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of oral suspension contains 5 mg of riluzole

Excipients with known effects: 1 ml of oral suspension contains 400 mg of sorbitol E420 (equivalent to 571.43 mg of liquid sorbitol (70%w/w).

3 PHARMACEUTICAL FORM

Oral suspension

Slightly brown, opaque homogeneous suspension after being manually shaken.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TEGLUTIK is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

Clinical trials have demonstrated that riluzole extends survival for patients with ALS (see section 5.1). Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free.

There is no evidence that TEGLUTIK exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. TEGLUTIK has not been shown to be effective in the late stages of ALS.

Safety and efficacy of TEGLUTIK has only been studied in ALS. Therefore, TEGLUTIK should not be used in patients with any other form of motor neurone disease.

4.2 Posology and method of administration

Treatment with TEGLUTIK should only be initiated by specialist physicians with experience in the management of motor neurone diseases.

Posology

The recommended daily dose in adults or elderly is 100 mg (50 mg every 12 hours). No significant increased benefit can be expected from higher daily doses.

It is recommended to assume 10 ml two times a day of the suspension (i.e. 10 ml corresponds to 50 mg of Riluzole).

Special populations

Paediatric population:

TEGLUTIK is not recommended for use in paediatric population, due to a lack of data on the safety and efficacy of riluzole in any neurodegenerative diseases occurring in children or adolescents.

Patients with impaired renal function:

TEGLUTIK is not recommended for use in patients with impaired renal function, as studies at repeated doses have not been conducted in this population (see section 4.4).

Older people:

based on pharmacokinetic data, there are no special instructions for the use of TEGLUTIK in this population.

Patients with impaired hepatic function:

see section 4.3, section 4.4, and section 5.2.

Method of administration

The suspension can be given per oral administration and alternatively it is also suitable for administration via enteral feeding tubes.

Dilution with liquids is not necessary.

The suspension is administered by means of graduated dosing syringe.

For instructions on handling of the product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to 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 breast-feeding.

4.4 Special warnings and precautions for use

Liver impairment:

Riluzole 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/SGOT 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 riluzole (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.

Riluzole should be discontinued if the ALT levels increase to 5 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.

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 riluzole in case of neutropenia (see section 4.8).

Interstitial lung disease

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

Renal impairment:

Studies at repeated doses have not been conducted in patients with impaired renal function (see section 4.2).

This medicine contains 4000 mg sorbitol (E420) in 10 ml of oral suspension.

The additive effect of concomitantly administered products containing sorbitol and dietary intake of sorbitol should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Patients with hereditary problems of fructose intolerance should not take this medicine.
This medicine contains less than 1 mmol sodium(23 mg) per 10 ml of oral suspension, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no clinical studies to evaluate the interactions of riluzole with other medicinal products.
In vitro studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole. Inhibitors of CYP 1A2 (e.g. caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones) could potentially 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
TEGLUTIK is contraindicated in pregnancy (see section 4.3 and 5.3). Clinical experience with riluzole in pregnant women is lacking.

Breast-feeding
TEGLUTIK is contraindicated in breast-feeding women (see section 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 or operate machinery if these symptoms occur.

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

4.8 Undesirable effects

Summary of safety profile
In phase III clinical studies conducted in ALS patients treated with riluzole, the most commonly reported adverse reactions were asthenia, nausea and abnormal liver function tests.

Tabulated summary of adverse reactions
Undesirable effects ranked under headings of frequency are listed below, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

	Very common	**Common**	**Uncommon**	**Not known**
Blood and lymphatic system disorders			Anaemia	Severe neutropenia (see section 4.4)
Immune system disorders			Anaphylactoid reaction, angioedema	
Nervous system disorders		Headache, dizziness, oral paraesthesia, somnolence		
Cardiac disorders		Tachycardia		
Respiratory, thoracic and mediastinal disorders			Interstitial lung disease (see section 4.4)	
Gastrointestinal disorders	Nausea	Diarrhoea, abdominal pain, vomiting	Pancreatitis	
Skin and subcutaneous tissue disorders				Rash
Hepato-biliary disorders	Abnormal liver function tests			Hepatitis
General disorders and administration site	Asthenia	Pain		

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).

Study data indicate that Asian patients may be more susceptible to liver function test abnormalities - 3.2% (194/5995) of Asian patients and 1.8% (100/5641) of Caucasian patients.

Riluzole oral suspension

Riluzole oral suspension and riluzole tablets total exposure was bioequivalent, while mean Cmax (the maximally achieved blood concentration of riluzole after ingestion) of the oral suspension was approximately 20% higher than mean Cmax of the riluzole tablets (see section 5.2).

There may be a slightly higher risk of the adverse events (e.g. dizziness, diarrhoea, asthenia and ALT increase) with the oral suspension.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Neurological and psychiatric symptoms, acute toxic encephalopathy with stupor, coma, and methemoglobinemia have been observed in isolated cases.

In case of overdose, treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other nervous system drugs, ATC code: N07XX02.

Mechanism of action

Although the pathogenesis of ALS is not completely elucidated, it is suggested that glutamate (the primary excitatory neurotransmitter in the central nervous system) plays a role for cell death in the disease.

Riluzole is proposed to act by inhibiting glutamate processes. The mode of action is unclear.

Clinical efficacy and safety

In a 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. Survival, as defined in the second paragraph of section 4.1, was significantly extended 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.

In a 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 higher compared to patients who received placebo. The effect of riluzole 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. The median survival time approached 16.5 months versus 13.5 months for riluzole 100 mg/day and placebo, respectively.

In a parallel group study designed to assess the efficacy and safety of riluzole in patients at a late stage of the disease, survival time and motor function under riluzole did not differ significantly from that of placebo. In this study the majority of patients had a vital capacity less than 60%.

In a double-blind placebo-controlled trial designed to assess the efficacy and safety of riluzole in Japanese patients, 204 patients were randomised to riluzole 100 mg/day (50 mg 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. However, the power of this study to detect differences between treatment groups was low. Meta-analysis including this study and those described above showed a less striking effect on survival for riluzole as compared to placebo although the differences remained statistically significant.

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

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%).

In a bioequivalence study the total exposure of riluzole 50 mg tablets and riluzole 5 mg/ml oral suspension were equivalent. (Ratio: 106.84%; 90% CI: 96.98-117.71%). Riluzole is more rapidly absorbed after the administration of oral suspension (Tmax approximately 30 minutes) with a Cmax approximately 20% higher than after the administration of riluzole tablets (Ratio: 122.32%; 90% CI: 103.28-144.88%). (see section 4.8).

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 metabolism of riluzole. The metabolites identified in urine are three phenolic derivatives, one ureido-derivative and unchanged riluzole.

The primary metabolic pathway for riluzole is initial oxidation by cytochrome P450 1A2 producing Nhydroxy-riluzole (RPR1 12512), 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.

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 $ml.min^{-1}$) 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 elderly (> 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 conducted to evaluate the pharmacokinetics of riluzole and its metabolite N-hydroxyriluzole 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 ($_{(Cmcx}$ *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.

Gender:

a bioequivalence study has been conducted between TEGLUTIK° (oral suspension) and RILUTEK° (tablets). The results showed bioequivalence between both formulations in female subjects while a higher exposure in terms of Cmax and AUC of riluzole was observed in male subjects.

However, no relevant clinical impact is expected.

5.3 Preclinical safety data

Riluzole did not show any carcinogenicity potential in either rats or mice.

Standard tests for genotoxicity performed with riluzole were negative. Tests on the major active metabolite of riluzole gave positive results in two in vitro tests. Intensive testing in seven other standard *in vitro* or *in vivo* assays did not show any genotoxic potential of the metabolite. On the basis of these data, and taking into consideration the negative studies on the

carcinogenesis of riluzole in the mouse and rat, the genotoxic effect of this metabolite is not considered to be of relevance in humans.

Reductions in red blood cell parameters and/or alterations in liver parameters were noted inconsistently in subacute and chronic toxicity studies in rats and monkeys. In dogs, haemolytic anaemia was observed.

In a single toxicity study, the absence of corpora lutea was noted at a higher incidence in the ovary of treated compared to control female rats. This isolated finding was not noted in any other study or species.

All these findings were noted at doses which were 2-10 times higher than the human dose of 100 mg/day.

In the pregnant rat, the transfer of ^{14}C- riluzole across the placenta to the foetus has been detected. In rats, riluzole decreased the pregnancy rate and the number of implantations at exposure levels at least twice the systemic exposure of humans given clinical therapy. No malformations were seen in animal reproductive studies.

In lactating rats, ^{14}C-riluzole was detected in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid Sorbitol (E420)
Aluminium magnesium Silicate
Xanthan Gum (E415)
Saccharin Sodium (E954)
Simethicone emulsion 30%
Sodium Laurilsulphate
Macrogol Cetostearyl Ether
Water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

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 Riluzole 5 mg/mL Oral Suspension.

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Teglutik Oral Suspension is suitable for oral administration and alternatively it is also suitable for administration via enteral feeding tubes.

Instruction for oral administration

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, wash the syringe with tap water.

Instructions for administration via enteral feeding tubes

Teglutik Oral Suspension is suitable for use with enteral feeding tubes.

The compatibility has been tested with tubes of silicone or polyurethane with diameters from 14Fr to 20 Fr.

It is recommended to follow the instruction below:

Ensure that the enteral feeding tube is free from obstruction before administration.

1. Flush the enteral tube with 30 ml of water

2. Administer the required dose of Teglutik oral suspension with a graduated dosing syringe

3. Flush the enteral tube with 30 ml of water.

7 MARKETING AUTHORISATION HOLDER

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