RILUZOLE 50 MG FILM-COATED TABLETS
(Riluzole)
PL 24668/0211

UKPAR

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LAY SUMMARY

The MHRA granted Caduceus Pharma Ltd a Marketing Authorisation (licence) for the medicinal product Riluzole 50 mg film-coated tablets on 21 February 2011. This product is available as a prescription-only medicine (POM) for the treatment of people who have a disease of the nervous system affecting their muscle strength called amyotrophic lateral sclerosis.

Riluzole 50 mg film-coated tablets contain the active substance riluzole, which is a nervous system medicine.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Riluzole 50 mg film-coated tablets outweigh the risks, hence a Marketing Authorisation has been granted.
RILUZOLE 50 MG FILM-COATED TABLETS

PL 24668/0211

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Caduceus Pharma Ltd, a Marketing Authorisation for the medicinal product Riluzole 50 mg film-coated tablets (PL 24668/0211) on 21 February 2011. This product is available as a prescription-only medicine (POM) and is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

This is a standard abridged application submitted under Article 10(1) of Directive 2001/83/EC, as amended claiming to be a generic medicinal product of Rilutek 50 mg Film-coated Tablets (Aventis Pharma S.A), which has been authorised in the EEA since 10 June 1996.

This product contains the active ingredient riluzole which belongs to a pharmacotherapeutic group of drugs called ‘other nervous system drugs’ (ATC code: N07X X02).

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.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support this application, comparing the test product Riluzole 50 mg film-coated tablets (Caduceus Pharma Ltd, UK) and the reference product Rilutek 50 mg Film-coated Tablets (Aventis Pharma S.A, France). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The MHRA considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for the non-submission of a Risk Management Plan.

No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of taking Riluzole 50 mg film-coated tablets outweigh the risks; hence a Marketing Authorisation has been granted.
ACTIVE SUBSTANCE

INN: Riluzole
Chemical names: 6-(trifluoromethoxy)-2-benzothiazolamine

Structure:

![Structure Diagram]

Molecular formula: C₈H₅F₃N₂OS
Molecular weight: 234.20
Description: White to slightly yellow powder
Solubility: Freely soluble in acetone, methanol, acetonitrile, ethanol, isopropanol, glacial acetic acid, ethyl acetate, dichloromethane, toluene, slightly soluble in hexane and very slightly soluble in water.

Riluzole is not the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
**MEDICINAL PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely anhydrous calcium hydrogen phosphate, maize starch, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and Opadry White 03F28689 (consisting of hypromellose, macrogol and titanium dioxide).

Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Opadry White 03F28689, which is compliant with suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical development**

The aim of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of Rilutek 50 mg Film-coated Tablets (Aventis Pharma S.A).

Suitable pharmaceutical development data have been provided for this application.

Comparable *in vitro* dissolution and impurity profiles have been provided for the proposed and originator product.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished product specification**

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

The product is packaged in aluminium/aluminium or aluminium/polyvinylchloride blisters in pack sizes of 1, 14, 28, 30, 56 or 60 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submit the mock-ups to the UK regulatory authority for approval before marketing.
Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months with no special storage conditions is set and is acceptable.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Expert Report
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a marketing authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that the proposed product is a generic medicinal product of an originator product that has been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of riluzole is well-known. With the exception of the bioequivalence study, no pharmacokinetic or pharmacodynamic data were submitted for this application, and none were required for an application of this type.

The following bioequivalence study was submitted:

A randomised, open label, two treatment, two period, two sequence, single dose, crossover study, comparing the pharmacokinetics of the test product Riluzole 50 mg film-coated tablets (Caduceus Pharma Ltd, UK) versus the reference product Rilutek 50 mg Film-coated Tablets (Aventis Pharma S.A, France) in healthy, adult, non-smoking volunteers under fasting conditions.

Subjects were administered a single oral dose of 50 mg riluzole of the test or the reference product with 240 ml of water after an overnight fast of at least 10 hours. Blood samples were collected pre- and up to 72 hours post dose. The treatment phases were separated by a washout period of at least 13 days.

The main pharmacokinetic results for riluzole are presented below (arithmetic means, ratio and confidence intervals [CI]):

<table>
<thead>
<tr>
<th></th>
<th>Test product</th>
<th>Reference product</th>
<th>Test/Ref Ratio (%)</th>
<th>90% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-t}$ (ng/ml*h)</td>
<td>620.984</td>
<td>640.410</td>
<td>1.00</td>
<td>95% - 105%</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng/ml*h)</td>
<td>653.476</td>
<td>674.583</td>
<td>0.99</td>
<td>95% - 104%</td>
</tr>
<tr>
<td>C$_{\text{max}}$ (ng/ml)</td>
<td>138.840</td>
<td>141.204</td>
<td>1.01</td>
<td>91% - 112%</td>
</tr>
</tbody>
</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{\text{max}}$ maximum plasma concentration
90% CI calculated from log transformed data

The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1041/98) defines the confidence limits as 80% to 125% for C$_{\text{max}}$ and AUC values. The 90% confidence intervals of the test/reference ratio for the log-transformed parameters C$_{\text{max}}$, AUC$_{0-t}$ and AUC$_{0-\infty}$ lie within acceptable limits. Thus the data support the claim that the test product Riluzole 50 mg film-coated tablets (Caduceus Pharma Ltd, UK) is bioequivalent to the reference product Rilutek 50 mg Film-coated Tablets (Aventis Pharma S.A, France).

EFFICACY
No new efficacy data have been submitted and none are required for an application of this type.

SAFETY
No new safety concerns were highlighted during the pharmacokinetic study.
EXPERT REPORT
A clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The SmPC is clinically satisfactory and is consistent with that for the reference product.

Patient Information Leaflet (PIL)
The PIL is satisfactory and consistent with the SmPC.

Labelling
The labelling is satisfactory.

CONCLUSION
The applicant has demonstrated that this product and its reference product are bioequivalent. It is recommended that a marketing authorisation is granted for this application.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Riluzole 50 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of riluzole are well-known, no additional data were required.

Efficacy
Bioequivalence has been demonstrated between the applicant’s Riluzole 50 mg film-coated tablets and the respective reference product, Rilutek 50 mg Film-coated Tablets (Aventis Pharma S.A, France).

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with riluzole is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is therefore considered to be positive.
RILUZOLE 50 MG FILM-COATED TABLETS
PL 24668/0211

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 18 June 2009.

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 03 July 2009.

3. Following assessment of the application the MHRA requested further information relating to the clinical dossier on 10 September 2009 and 21 July 2010 and the quality dossier on 26 October 2009 and 25 June 2010.

4. The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 15 September 2009 and 28 July 2010 and the quality dossier on 16 June 2010 and 16 July 2010.

5. The application was determined on 21 February 2011.
RILUZOLE 50 MG FILM-COATED TABLETS

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STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Riluzole 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 50 mg of riluzole.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White or off-white, oval and biconvex film-coated tablets with a dimension of 5.2 x 10 mm and marked “RL 50” on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Riluzole 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 riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. Riluzole has not been shown to be effective in the late stages of ALS.
Safety and efficacy of riluzole has only been studied in ALS. Therefore, riluzole should not be used in patients with any other form of motor neurone disease.

4.2 Posology and method of administration
Treatment with riluzole should only be initiated by specialist physicians with experience in the management of motor neurone diseases.
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.

Special populations
Children: Riluzole is not recommended for use in children, 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: Riluzole 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).

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

Patients with impaired hepatic function: (see section 4.3, section 4.4, and section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
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 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.

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

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

Riluzole is contraindicated (see section 4.3) in breast-feeding women (see section 5.3).
It is not known whether riluzole is excreted in human milk.

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
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.

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).

**Blood and the lymphatic system disorders**
*Uncommon:* anaemia
*Not known:* severe neutropenia (see section 4.4)

**Immune system disorders**
*Uncommon:* anaphylactoid reaction, angioedema

**Nervous system disorder**
*Common:* headache, dizziness, oral paraesthesia and somnolence

**Cardiac disorders**
*Common:* tachycardia

**Respiratory, thoracic and mediastinal disorders**
*Uncommon:* interstitial lung disease (see section 4.4)

**Gastrointestinal disorders**
*Very common:* nausea
*Common:* diarrhoea, abdominal pain, vomiting
*Uncommon:* pancreatitis

**Hepato-biliary disorders**
*Very common:* abnormal liver function tests. 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 ULN, treatment was discontinued and the levels returned to less than 2 times ULN within 2 to 4 months in most cases (see section 4.4).
*Not known:* hepatitis

**General disorders and administration site conditions**
*Very common:* asthenia
*Common:* pain

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

No specific antidote or information on treatment of overdosage with riluzole is available.

In case of overdose, treatment is symptomatic and supportive.

### 5 PHARMACOLOGICAL PROPERTIES
#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other nervous system drugs, ATC code: N07XX02.

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 trials**
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 ($C_{\text{max}} = 173 \pm 72$ (sd) ng/ml). About 90% of the dose is absorbed and the absolute bioavailability is $60 \pm 18\%$.
The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in $C_{\text{max}}$ 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 $245 \pm 69$ l (3.4 l/kg). Riluzole is about 97% protein bound and it binds mainly to serum albumin and to lipoproteins.

Metabolism
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 N-hydroxy-riluzole (RPR112512), the major active metabolite of riluzole. This metabolite is rapidly glucurononoconjugated 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

Patients with 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.

Elderly: 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).

Patients with 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.

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.

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.

In the pregnant rat, the transfer of ¹⁴C-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, ¹⁴C-riluzole was detected in milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
- Calcium hydrogen phosphate, anhydrous
- Maize starch
- Croscarmellose sodium
- Silica colloidal, anhydrous
- Magnesium stearate

Tablet coating:
- Hypromellose
- Macrogol
- Titanium dioxide

6.2 Incompatibilities

Not applicable.
6.3 Shelf life
36 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
The tablets are packaged in aluminium/aluminium or aluminium/PVC blisters.

Pack sizes:
1, 14, 28, 30, 56 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street, London W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0211

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/02/2011

10 DATE OF REVISION OF THE TEXT
21/02/2011
PACKAGE LEAFLET: INFORMATION FOR THE USER

Riluzole 50 mg film-coated tablets
Riluzole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Riluzole is and what it is used for
2. Before you take Riluzole
3. How to take Riluzole
4. Possible side effects
5. How to store Riluzole
6. Further information

1. WHAT RILUZOLE IS AND WHAT IT IS USED FOR

Riluzole is a nervous system medicine.

Riluzole has been prescribed by your doctor for a disease of the nervous system affecting your muscle strength called amyotrophic lateral sclerosis. Your doctor may give you further information about why this medicine has been prescribed for you.

2. BEFORE YOU TAKE RILUZOLE

Do not take Riluzole
- if you are allergic (hypersensitive) to riluzole or any of the other ingredients of riluzole,
- if you have any liver disease or abnormal elevations of some enzymes of the liver (transaminases),
- if you are pregnant or breast-feeding.

Take special care with Riluzole
- if you experience increased blood levels of some enzymes of the liver (transaminases), your doctor will do regular blood tests to follow this during treatment and will take the necessary measures, because of the risk of hepatitis.
- if you experience any fever (increase in temperature), you must call your doctor immediately. This may be a sign of decrease in the number of white blood cells which are important in fighting infections.
- if you have any kidney disease, you should tell your doctor.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
If you are pregnant or think you are, you must NOT take riluzole. You must NOT breast-feed if you are taking riluzole.
If you think you are pregnant or could become pregnant, discuss this matter with your doctor. Also discuss with your doctor if you intend to breast-feed.

**Driving and using machines**
Do not drive or use machines if you have vertigo or feel dizzy when you take riluzole.

3. **HOW TO TAKE RILUZOLE**

The recommended dose is one tablet twice a day. You should take this medicine orally on a regular basis, every 12 hours, at the same time of the day (e.g. in the morning and evening) each day.

There is no benefit in increasing the dose above 2 tablets per day. However, you may encounter more side effects.

**If you take more Riluzole than you should**
If you have accidentally taken too many tablets, contact your doctor.

**If you forget to take Riluzole**
If you forget to take your tablet, take the next tablet as originally planned. Do not take a double dose to make up for a forgotten tablet.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, riluzole can cause side effects, although not everybody gets them.

**IMPORTANT**
Tell your doctor immediately
- If you experience any fever (increase in temperature) because RILUZOLE may cause a decrease in the number of white blood cells. Your doctor may want to take a blood sample to check the number of white blood cells, which are important in fighting infections.

- If you experience any of the following symptoms: yellowing of your skin or the white of your eyes (jaundice), itching all over, feeling sick, being sick, as these may be signs of liver disease (hepatitis). Your doctor may do regular blood tests while you are taking RILUZOLE to make sure that this does not occur.

- If you experience cough or difficulties in breathing, as this may be a sign of lung disease (called interstitial lung disease).

The most common side effects (1 or more in 10 patients) of riluzole are tiredness, feeling sick and increased blood levels of some enzymes of the liver (transaminases) (see **BEFORE YOU TAKE RILUZOLE**).

The following side effects are common (between 1 in 10 and 1 in 100 patients): dizziness, sleepiness, headache, numbness or tingling of the mouth, increase in heart beat, abdominal pain, vomiting, diarrhoea, and pain.

The uncommon side effects (between 1 in 100 and 1 in 1000 patients) of riluzole are: anaemia, allergic reactions, inflammation of the pancreas (pancreatitis) and interstitial lung disease.

Decreases in the number of white blood cells (which are important in fighting infections) and liver disease (hepatitis) may occur (see **BEFORE YOU TAKE RILUZOLE**).
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE RILUZOLE**

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use riluzole after the expiry date which is stated on the carton and the blister.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

What Riluzole contains

- The active substance is riluzole 50 mg.
- The other ingredients are: calcium hydrogen phosphate anhydrous, maize starch, croscarmellose sodium, silica colloidal, anhydrous, magnesium stearate, hypromellose, macrogol and titanium dioxide.

What Riluzole looks like and contents of the pack

Riluzole are white or off-white, oval and biconvex film-coated tablets with the dimensions of 5.2 x 10 mm and marked RL 50 on one side.

**Pack sizes:**

Blisters:
1, 14, 28, 30, 56 and 60 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**

Cadeceus Pharma Ltd.
6th Floor, 94 Wigmore Street, London W1U 3RF
United Kingdom

**Manufacturer:**

Actavis Iif.
Reykjavikurvegi 78,
P.O. Box 420,
IS-222 Hafnarfjordur
ICELAND

This leaflet was last approved in 02/2011.
# LABELLING

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| OUTER CARTON for blisters |

## 1. NAME OF THE MEDICINAL PRODUCT

Riluzole 50 mg film-coated tablets  

rilmazole

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg of riluzole.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

1 tablet  
14 tablets  
28 tablets  
30 tablets  
56 tablets  
60 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use  
Read the package leaflet before use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

Exp:

## 9. SPECIAL STORAGE CONDITIONS
This medicinal product does not require any special storage conditions

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Cudenceus Pharma Ltd.
6th Floor, 94 Wigmore Street, London W1U 3RF
United Kingdom

12. MARKETING AUTHORIZATION NUMBER(S)

PL 24668/0211

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

[POM]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

riluzole 50 mg film-coated tablets
| MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS |
| BLISTER (ALUMINIUM/ALUMINIUM AND ALUMINIUM/PVC) |

| 1. NAME OF THE MEDICINAL PRODUCT |
| Riluzole 50 mg film-coated tablets |
| riluzole |

| 2. NAME OF THE MARKETING AUTHORISATION HOLDER |
| Caduceus Pharma Ltd. |

| 3. EXPIRY DATE |
| Exp: |

| 4. BATCH NUMBER |
| Lot: |

| 5. OTHER |