IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1380/020/001
Case No: 2043951

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Riluzole Actavis 50 mg film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/05/2009** until **27/05/2014**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Riluzole Actavis 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 marked RL 50 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Riluzole Actavis 50 mg film-coated tablets 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 Actavis 50 mg film-coated tablets 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.

Pregnancy 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).

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, 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 Pregnancy and lactation

Riluzole Actavis 50 mg film-coated tablet is contraindicated (see section 4.3) in pregnancy (see section 5.3). Clinical experience with riluzole in pregnant women is lacking.

Riluzole Actavis 50 mg film-coated tablet 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

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

Hepatobiliary 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

* 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.

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_{max} = 173 ± 72 (sd) ng/ml). About 90% of the dose is absorbed and the absolute bioavailability is 60 ± 18%.
The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in C_{max} of 44%, decrease in AUC of 17%).

Distribution
Riluzole is extensively distributed throughout the body and has been shown to cross the blood brain barrier. The volume of distribution of riluzole is about 245 ± 69 l (3.4 l/kg). Riluzole is about 97% protein bound and it binds mainly to serum albumin and to lipoproteins.

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 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
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.

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 (Cmax 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.

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 ^{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

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

Tablet coating OPADRY AMB white 03F28689 consisting of:
Hypromellose
Macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Blisters (aluminium/aluminium): This medicinal product does not require any special storage conditions.
Blisters (aluminium/PVC): Keep the blister in the outer carton in order to protect from light. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blisters (aluminium/aluminium) or blisters (aluminium/PVC), pack sizes of 28, 30, 56 and 60 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/20/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 28th May 2009

10 DATE OF REVISION OF THE TEXT