VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Amyotrophic lateral sclerosis (ALS) is fatal and rare but the most common motor neuron disease. Symptoms are progressive muscle loss and weakness, tiredness and problems with swallowing, which typically lead to severe breathing problems and eventually death. In addition, difficulty with speaking and uncontrollable salivation are symptoms of this disease. Life expectancy is 2 to 4 years from onset, only 5–10% of patients survive beyond 10 years (Chiò et al, 2009).

The incidence of ALS is one or two out of 100,000 people each year, generally affecting men between 55 and 65 years of age (approximately 30,000 are Americans). The disease seems to be race specific with a prevalence estimated at 1.2-4.0 per 100,000 Caucasians individuals with a lower rate in other ethnic populations (Logrosino

et.al, 2010). As this population ages, the prevalence increases. Many researchers think that ALS is caused by a combination of genetic and environmental risk factors, although only age has been linked to ALS.

VI.2.2 Summary of treatment benefits

A majority of patients are stricken with this disease at the prime of their lives. Because there is no cure, riluzole is a medication that helps people live longer and comfortably. Although not clearly proven, riluzole has been shown to improve the quality of life. Clinical trials have shown that patients who received riluzole as compared to patients who received placebo survive longer without intubation. If the dosage was increased from 50 mg/day to 200 mg/day patient survival remained the same.

VI.2.3 Unknowns relating to treatment benefits

There is a lack of safety and efficacy data of the effect of riluzole in regards to any neurodegenerative disease, particularly in children and adolescents under 18 years of age or in reproductive performance and fertility. Transfer from mother to foetus during pregnancy or nursing children is unknown. Individuals with kidney problems should avoid riluzole due to the absence of research data.

VI.2.4 Summary of safety concerns

Table 23 Important identified risks

Important Identified Risk	What is known	Preventability
Rapid heartbeat (Tachycardia)	The development of a rapid heartbeat with riluzole treatment is common.	Patients with a history of heart problems should be closely followed by their physician when prescribed this drug.
Liver disease (Liver Impairment)	Abnormal liver function tests are very common in patients using riluzole. Riluzole should be prescribed with care in patients with a history of liver problems, or those with slightly higher amounts of liver enzymes that break down amino acids (ALT/SGPT; AST/SGOT up to 3 times the upper limit of the normal range (ULN)), as well as increased amount waste products from cells in the bloodstream.	Several liver function tests should be done to determine if changes in liver enzyme production and cell waste products that appear in the bloodstream (especially elevated bilirubin) has increased after riluzole treatment.
Low white blood cell count (Neutropenia)	A decrease in white blood cell count is very rare. Only a few cases have shown that riluzole treatment can decrease white blood cell numbers in the bloodstream.	If patients develop fever after taking riluzole, they should immediately tell their physician. Physicians should then check white blood cell counts and discontinue riluzole.
Inflammation of the tissue and space around the air sacs of the lungs (Interstitial lung disease)	Cases of interstitial lung disease have been reported in patients treated with riluzole, some of them were severe. In the majority of the reported cases, symptoms disappeared after treatment with riluzole was stopped.	If respiratory symptoms develop such as dry cough and/or dyspnoea, chest radiography should be performed. If testing shows this risk to be related to riluzole prescription, this drug should be discontinued immediately.
Breakdown of red blood cells (Haemolytic anaemia)	This risk fairly uncommon in patients. However, in preclinical	Patients with a history of certain blood disorders should be

Important Identified Risk	What is known	Preventability
	studies, the breakdown of red blood cells was found in dogs given riluzole. Depending on where this break down occurs in the body, it can be either harmless or life-threatening. Noticeable symptoms can such as tiredness and shortness of breath. Symptoms that may be more difficult to discern may be jaundice, gallstones or high blood pressure.	monitored closely. The known symptoms that have been previously described should be the priority of the attending physician.
Allergic reactions that may include rash, swelling of the throat (Hypersensitive reactions including anaphylactoid reaction)	These type of reactions are uncommon in patients who have been or are currently prescribed rilzulole. There may be some type allergic reaction to some of the ingredients other than the drug itself.	The attending physician should be aware of patient history in regards to allergic reactions. Individuals under treatment of riluzole should be closely monitored for possible hypersensitive reactions.
Swelling of the skin (Angioedema)	Swelling of the skin of patients prescribed riluzole is an uncommon reaction.	The attending physician should be aware of patient history in regards to allergic reactions. Individuals under treatment of riluzole should be closely monitored for possible hypersensitive reactions.
Stomach pain, back pain, nausea, vomiting as a result of an inflamed pancreas (Pancreatitis)	Inflammation of the pancreas that may lead to stomach pain, nausea and vomiting in patients prescribed riluzole is an uncommon reaction.	If these symptoms occur the patient should immediately seek a physician.
Dizziness and vertigo	Dizziness is common in patients who have taken riluzole.	Although there have been no studies conducted on the effect of riluzole on the ability to drive and use machinery, patients should be warned about the potential for dizziness or vertigo, and advised not to drive or operate machinery if these symptoms occur.

Table 24 Important potential risks

Important Potential Risk	What is known (including reason why it is considered a potential risk)
Liver inflammation (Hepatitis)	Although the risk of hepatitis is unknown, abnormal liver tests results are common which may be the first signs of inflammation. Liver enzymes should be measured before and during therapy with riluzole especially in patients with increased liver enzyme levels. Testing should be done monthly during the first 3 months of treatment, every 3 months during the remainder of the first year and periodically thereafter.
Maternal and embryo/foetal toxicity	Information regarding the effect of riluzole during pregnancy on the child and mother is unknown. Riluzole should not be administered to patients who are pregnant or breast-feeding. Preclinical studies of pregnant rats, found that riluzole given at twice the dosage normally given to humans crossed the placenta to the foetus, decreased the pregnancy rate and the number of implantations of the

Important Potential Risk	What is known (including reason why it is considered a potential risk)
	egg. Pups that were born did not have obvious physical defects after treatment. In lactating rats, riluzole was detected in milk.
Interaction with other medicinal products inhibitors/inducers of the liver enzyme CYP1A2	Studies using human liver cells suggest that CYP 1A2 is the principal isoenzyme involved in the initial enzyme that acts on riluzole. Many drugs can act against CYP 1A2 (e.g. caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones) which could potentially decrease the rate of riluzole released from the body, while inducers of CYP 1A2 (e.g. cigarette smoke, charcoal-broiled food, rifampicin and omeprazole) could increase the rate of riluzole elimination. There have been no clinical studies to evaluate the interactions of riluzole with other medicinal products.
Effects on the 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. It should be noted that no studies on the effects on the ability to drive and use machines have been performed.

Table 25 Missing information

Missing Information	What is known
Safety in pregnancy/breast-feeding	Information regarding the effect of riluzole on the child and mother during pregnancy is unknown. In addition, there is medical information that states that riluzole is found in the milk of breastfeeding women.
Safety and efficacy in children and adolescents under 18 years of age	No medical studies have been done to determine the effect of riluzole treatment on children under the age of 18.
Effect on reproductive performance and fertility	Fertility studies in rats showed minor problems in reproductive performance at doses higher than those usually prescribed to humans. This was probably due to decreased activity of the animals at this dose. No medical studies have been done to determine the effect of riluzole treatment on women who are attempting to become pregnant.
Kidney problems (Use in patients with impaired renal function)	Patients whose kidneys do not function properly should not use riluzole since studies have not been done determining the effect of numerous dose taken over time.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Table 26 Major changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment
1.0		-	The initial RMP.
1.1	26.2.2015	Version of RMP last submitted **Part I-Overview** Revision Indication and Posology Exact indication mentioned Contraindication and warnings in patients Pharmaceutical form and strengths authorised Dates of authorisation/launch amended Module SV Post-authorisation experience Module SVIII amended Safety concerns Part V-RMM amended to Module SVIII PSURs added to RMM, "How effectiveness of RMM… Impact of risk minimisation for safety concerns amended Entering of adverse event in section 4.8 amended as the routine for specific safety concern. Updated table 16 according to comments on safety concerns Part VI Table 17	The relevant sections of the RMP were revised to implement the supplementary information requested by SUKL.

		amended Summary table of RMM, Table 18 amended Overview of disease epidemiology added “problems speech and salivation” Summary treatment benefits amended Unknowns relating to treatment benefits amended Table 19 amended according to the comments in SVIII	