Licensed Indication:
Riluzole is indicated ‘to extend life, or the time to mechanical ventilation, for patients with amyotrophic lateral sclerosis (ALS)’

‘Riluzole should not be used in any other form of motor neurone disease’ (MND).

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

Background information
Amyotrophic lateral sclerosis, is a variant of motor neurone disease, a progressive, fatal neurodegenerative disorder. It is characterised by progressive loss of motor neurones, resulting in muscle weakness, amyotrophy, fasciculation and bulbar involvement. Death usually results from respiratory failure.2,3

ALS is the most common form of MND. It occurs worldwide, affects all races and has a consistent male:female ratio of 1.5:1. The incidence is approximately 2 per 100,000 with a prevalence in the range of 4-5 per 100,000.4,5 This suggests approximately 220 people in the West Midlands region currently have ALS. Young adults may be affected but the disease predominantly affects patients of 60 years and older.

ALS is usually sporadic, however up to 10% of presenting cases have a family history. 70% of patients with ALS present with progressive asymmetrical weakness of the limbs (limb onset), 25% with bulbar symptoms and approximately 3% with respiratory failure. The average life expectancy is 4 years for those with limb onset and 2 years for those with bulbar onset disease. 20% of patients will survive more than 5 years and 5% more than 10 years.2,3,4

Current treatment options
Symptomatic management, supportive, and palliative care are available for patients with MND. These are tailored to the individuals needs at any given time in their disease process.

Riluzole is the only drug currently licensed for the treatment of ALS.

Clinical Efficacy
The clinical effectiveness of riluzole in the treatment of ALS has been evaluated systematically in a Health Technology Assessment undertaken for the National Institute for Clinical Excellence (NICE). This evaluation considered data from four randomised, double blind placebo-controlled studies. These trials were undertaken in a total of 1477 patients with ALS. Doses of riluzole studied ranged from 50 – 200mg/day. Three trials investigated riluzole at 100mg/day, and one used doses of 50mg, 100mg and 200mg/day.6

The primary outcome in each study was tracheostomy-free survival, defined as the time to tracheostomy or death. Other endpoints included muscle strength, limb function and bulbar function.

Combined results demonstrate that riluzole was associated with a relative reduction in hazard ratio for tracheostomy-free survival at 18 months of 17% (hazard ratio of 0.88, 95% CI 0.75 – 1.02). There was some heterogeneity across the results of these four trials.5 Estimates from two of the trials suggest a gain in median tracheostomy free survival of 2 to 4 months.5,6

Subgroup analysis by site of onset (bulbar vs limb) identifies no clear evidence of any interaction between treatment effect and site of onset.6

A pooled analysis of the effect of treatment on functional status suggests a small reduction in the rate of deterioration of functional outcomes. It is not clear whether these differences are clinically significant.6

No comparative data are available for long-term treatment outcomes.

Adverse Effects
In clinical trials between 6-25% of patients withdrew from riluzole due to side effects compared with 7-21% treated with placebo.5

Adverse events occurring more commonly with riluzole than placebo in clinical trials included asthenia, nausea, vomiting, abdominal pain, headache, pain, dizziness, tachycardia, somnolence and circumoral paraesthesia.1,6
Increases in alanine aminotransferase (ALT) levels were also reported. Regular monitoring of serum transaminases is advised during treatment; monthly during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter. ALT levels should be monitored more frequently in patients who develop elevated levels. Riluzole treatment should be discontinued if ALT levels increase to five times the upper limit of normal.¹

Three cases of neutropenia have been recorded in 5000 patients who have received riluzole. White blood cell counts should be checked in patients with febrile illness. In the case of neutropenia riluzole should be discontinued.

NICE guidance
NICE issued guidance on the use of riluzole in January 2001.⁵

NICE has advised that:
- ‘Riluzole is recommended for the treatment of individuals with the amyotrophic lateral sclerosis (ALS) form of Motor Neurone Disease (MND).
- Riluzole therapy should be initiated by a neurological specialist with expertise in the management of MND. Routine supervision of therapy should be managed by locally agreed shared care protocols undertaken by general practitioners.’⁵

NICE consider that ‘in most cases, the specialist will be responsible for monitoring the progress of the disease and the safe use of riluzole. The needs of people with MND demand flexibility, and this monitoring role can be taken up by the general practitioner or by other physicians involved in providing shared care.’⁵

Cost
At current prices, one year’s treatment with riluzole 100mg/day costs £3,728.

Current estimates of the cost-effectiveness of riluzole must be viewed cautiously, since many uncertainties remain. Riluzole is associated with a net increased cost to the health service but the magnitude of this increase is difficult to predict with accuracy.⁵

Summary
Riluzole is the first drug available for the treatment of ALS. The efficacy of riluzole has been evaluated in four randomised controlled trials conducted in 1477 patients with ALS. The pooled analysis of the primary endpoint tracheostomy free survival did not reach the conventional levels of statistical significance. Benefits were however suggested in some of the individual studies. The true benefit of treatment is therefore not currently clear. It is very important that patients are fully informed before treatment is undertaken.

References