Specialised Medicine Service (SMS) Guideline ~

Riluzole for the treatment of individuals with the amyotrophic lateral sclerosis form of motor neurone disease

Specialist: Please complete letter at the end of this document and send together with a copy of this guideline to the GP.

GP: GPs are invited to participate. Please indicate whether you wish to share patient's care by completing letter at the end of this document and return to specialist.

Responsibilities remain with the specialist service until formally accepted by the GP. If a GP is not confident to undertake these roles, then they are under no obligation to accept. In such an event, the total clinical responsibility for the patient with the diagnosed condition remains with the specialist.

If the GP agrees to share the care of the patient, the patient should not be discharged from the care of their specialist, but rather the care of the patient will be shared between the patient, GP and specialist in accordance with the responsibilities outlined in this guideline.

The prescriber has the clinical and legal responsibility for the drug and the consequences of its use. Responsibility for drug monitoring and acting on results remains with the prescriber.

Introduction and aims of treatment

This Devon-wide guideline covers the use of riluzole to extend life or the time to mechanical ventilation for individuals with the amyotrophic lateral sclerosis (ALS) form of motor neurone disease. The guideline details the responsibilities for the ongoing prescribing and monitoring required to enable a shared care agreement to be arranged between the primary and secondary care interface. Refer to the online BNF and individual summaries of product characteristics (SPCs) for full prescribing data.

Riluzole is recommended by NICE Technology appraisal guidance [TA20], 2001. Riluzole therapy should be initiated by a neurological specialist with expertise in the management of motor neurone disease, following appropriate investigations.

The SPCs report that clinical trials have demonstrated that riluzole extends survival for patients with ALS; survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free. In addition, 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.

The SPCs also advise that safety and efficacy of riluzole has only been studied in ALS, thus riluzole should not be used in patients with any other form of motor neurone disease.

Specialist responsibilities

Specialists may decide to delegate some of these tasks to members of their team, however the responsibility for ensuring the following are undertaken remains with the named specialist overseeing the care of the individual patient:

- Assess the patient, establish diagnosis of ALS after appropriate investigations and the need for treatment with riluzole.
- Update records with list of existing drugs from available resources and ensure there are no drug interactions of clinical significance with current medication.
- Provide the patient and/ or the patient's carer with suitable written and verbal information about the medication prior to starting treatment, including benefits, side effects (particularly symptoms which may be suggestive of neutropenia or interstitial lung disease), frequency of dosing and monitoring requirements of treatment.
- Ensure the patient and/or the patient's carer understands that treatment may be stopped if they do not attend for monitoring & treatment review.

- Confirm patient and/or the patient's carer understands the treatment and record acceptance of associated patient responsibilities in the patient's medical records.
- Undertake pre-treatment screening and required baseline monitoring (see monitoring requirements below) and initiate riluzole for the management of ALS.
- **Prescribe riluzole and monitor treatment for the first 3 months of treatment, or until the patient's dose and blood tests are stabilised, whichever is longer, before sharing care with GP.**
- Prescribing and monitoring will remain in secondary care until the patient is stable and GP agrees to share care.
- Recommend that the patient and/ or the patient's carer consults a pharmacist before using over the counter (OTC) treatments.
- Ask the GP in writing whether they are willing to participate in shared care for a particular patient. Include all relevant test results (GPs may not have access to these results in primary care).
- **Specify review dates at clinically relevant time intervals for both the GP and the specialist.**
- During the review consider and discuss clinical effectiveness and adverse effects with the patient and/ or the patient's carer; evaluate the long-term benefit and whether medication is still indicated.
- Ensure prompt written summary is sent to the GP whenever the patient is reviewed including any changes in treatment or monitoring requirements, results of monitoring undertaken, assessment of adverse events, or guidance on when to stop treatment if indicated.
- Urgent changes to treatment should be communicated by telephone to GP and followed up in writing.
- Provide the GP with relevant contact information with clear arrangements for back-up advice and support.
- Ensure that the GP is informed in writing of any changes to the patient's specialist or their contact details.
- Respond promptly to the GP and advise on action required when abnormal monitoring results are identified or adverse effects signs or symptoms are detected.
- Reassume responsibility for prescribing and associated monitoring if a woman becomes or wishes to become pregnant.
- Report suspected side effects to the MHRA via yellow card scheme when appropriate.

General Practitioner responsibilities

GPs may decide to delegate some of these tasks to members of their team; however, the responsibility for ensuring the following are undertaken remains with the GP overseeing the care of the individual patient:

- Ensure a timely reply is sent to specialist in response to request for shared care.

If GP has agreed to share care:

- Be alert to the possibility of interactions when initiating new medicines or recommending over the counter (OTC) treatments.
- Continue to prescribe and monitor riluzole in accordance with these guidelines.
- Review monitoring results and take any necessary action (see monitoring requirements below).
- Ask the patient and/ or the patient's carer about adverse effects at every contact. Ensure prompt action in the case of a severe adverse effect or signs or symptoms (see monitoring requirements below).
- Ensure advice sought promptly from the specialist if there is a change in the patient's physical or mental health status which is of concern to the GP and may affect treatment, including pregnancy.
- Respond promptly to advice from specialist regarding any changes in treatment or monitoring requirements.
- Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.
- Where patient care is transferred from one GP practice to another a new shared care agreement must be completed.
- Report suspected side effects to the specialist and the MHRA via yellow card scheme when appropriate.

Patient and / or carer responsibilities

- Understand the importance of monitoring treatment and attend specialist and GP appointments to ensure timely monitoring can be completed in accordance with the prescribing guideline.
- Understand that treatment will be stopped if they do not attend for monitoring and treatment review.
- Read the riluzole patient information leaflet. Understand treatment, expected benefits and potential side effects. Request information in different format(s) if required to aid understanding.
- Take (or support administration of) medication as directed by the prescriber.
- Consult a pharmacist before using over the counter (OTC) treatments.
- Report any adverse events to the GP or specialist regarding their treatment, including cough and shortness of breath.
- Seek immediate medical attention if symptoms such as fever, rash, flu-like symptoms, sore throat, or oral ulceration present.
- Dizziness or vertigo, may affect performance of skilled tasks (e.g. driving). Do not drive or operate machinery if these symptoms occur.
- Women of child-bearing potential should take a pregnancy test if they think there is a possibility they could be pregnant, and inform the GP or specialist immediately if they become pregnant or wish to become pregnant.
- Store their medicines safely and securely at home and dispose of any unused medication appropriately.
- Report suspected side effects to the GP or specialist, and the MHRA via yellow card scheme when appropriate.

Monitoring requirements

Baseline assessment to be completed by the specialist:

- Baseline liver function, renal function and full blood count tests are recommended as a reference for subsequent monitoring.
- Before initiating treatment for women and girls of child-bearing potential it is essential to consider and discuss contraception and/ or, where appropriate, the risks of pregnancy (including risk to the foetus and risks associated with stopping or changing medication). If there is any possibility that the individual may be pregnant it is important to confirm this prior to starting treatment.

Monitoring to be completed by the specialist:

- Measure serum transaminases including alanine aminotransferase (ALT) and full blood count (FBC) every month during the first 3 months of treatment.
- Continue to measure serum transaminases every 3 months during the remainder of the first year and annually thereafter, **or** until shared care agreement is accepted, and ongoing prescribing and monitoring responsibilities are transferred to the GP.
- Respond promptly with advice on action required if adverse effects signs or symptoms are reported by the patient, either directly or through their GP.

Monitoring to be completed by the GP once shared care agreement in place:

The following monitoring should be performed by the GP; where abnormal results are identified consider the associated actions seeking advice from specialist for further support and guidance when required:

Test	Frequency	Result	Action to be taken by GP
Serum transaminases including ALT	Every 3 months during the remainder of the first year of treatment. Annually thereafter.	Elevated ALT levels: greater than 2 times the upper limit of normal	Continue riluzole. Discuss with specialist more frequent monitoring.
		Elevated ALT levels: 5 times the upper limit of normal	**Stop** riluzole immediately and seek prompt neurology advice.

Continuation of FBC monitoring is not usually required after the first 3 months of treatment; specialist will determine requirement on an individual patient basis.

Presentation of the following adverse effect symptoms and associated actions, should be noted:

Symptom	Action to be taken by GP
Dry cough and/or dyspnoea	• Arrange chest radiography • In the case of findings suggestive of interstitial lung disease (e.g. bilateral diffuse lung opacities) **stop** riluzole immediately • Seek prompt neurology review and inform them of findings
Febrile illness	• Perform white blood cell count • Treat febrile illness according to local pathways
Confirmed neutropenia (<1.5x 10^9/L)	• **Stop** riluzole immediately and seek prompt neurology review. • Review patient for signs and symptoms of infection and treat or refer according to local pathways, as appropriate.
Neutropenic sepsis suspected	• **Stop** riluzole immediately • Arrange immediate hospital assessment
Decreased white cell count to below lower limit of local reference range in the absence of febrile illness or clinical signs of neutropenia	• Seek advice from specialist.

Supporting Information

This section provides additional information regarding riluzole. Refer to the online BNF and SPCs for full prescribing data.

Dosage and administration

The licensed daily dose in adults is 50mg every 12 hours. No significant increased benefit can be expected from higher daily doses.

Riluzole is available as 50mg tablets and an oral suspension (5mg/1ml). Refer to Devon formulary for list of preparations approved for use in Devon. The suspension can be given orally; alternatively it is also suitable for administration via enteral feeding tubes (refer to SPC for supporting information). The oral suspension should be reserved for patients with swallowing difficulties or for enteral feeding tube administration due to the greater acquisition cost.

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), bilirubin and/or gamma-glutamyl transferase (GGT) levels. Baseline elevations of several liver function tests (especially elevated bilirubin) should preclude the use of riluzole.

Renal impairment:

Riluzole is not recommended for use in patients with impaired renal function, as studies at repeated doses have not been conducted in this population

Contraindications

- Hypersensitivity to riluzole 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
- Acute porphyrias (as reported by the BNF).

Adverse effects

This list is not exhaustive. Refer to the online BNF and SPCs for full prescribing data. Seek specialist advice where necessary.

Very common (≥1/10) or Common (≥1/100 to <1/10): abdominal pain, abnormal liver function tests, asthenia, diarrhoea, dizziness, drowsiness, headache, nausea, oral paraesthesia, pain, somnolence, tachycardia, vomiting

Uncommon (≥1/1,000 to <1/100): Anaemia, anaphylactoid reaction, angioedema, interstitial lung disease, pancreatitis

Not known: Hepatitis, severe neutropenia

Interactions

This list is not exhaustive. Refer to the online BNF and SPCs for full prescribing data. Seek specialist advice where necessary.

The following drug interactions are classified as moderate (the result could cause considerable distress or partially incapacitate a patient; they are unlikely to be life-threatening or result in long-term effects) and theoretical in the BNF, and are predicted to increase exposure to riluzole: **ciprofloxacin, combined hormonal contraceptives**, **fluvoxamine**, **mexiletine, osilodrostat, rucaparib** and **vemurafenib**.

The SPCs state that there have been no clinical studies to evaluate the interactions of riluzole with other medicinal products. The SPCs add that in vitro studies suggest that CYP1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole:

- The following inhibitors of CYP1A2 could potentially decrease the rate of riluzole elimination: **caffeine, diclofenac, diazepam, nicergoline, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline and quinolones**
- The following inducers of CYP1A2 could increase the rate of riluzole elimination: **cigarette smoke, charcoal-grilled food, rifampicin and omeprazole**.

Pregnancy and lactation

Riluzole is contraindicated in pregnancy and breast-feeding women. **Clinicians must check with up to date sources of information before prescribing in this area.**

The UK Teratology Information Service (UKTIS) provides a national service on all aspects of the toxicity of drugs and chemicals in pregnancy (Tel: 0344 892 0909), and provides the 'best use of medicines in pregnancy' (bumps) website for supportive information relating to individual treatments.

UK Drugs in Lactation Advisory Service (UKDILAS) provides evidence based information on the use of drugs during the breastfeeding period to all UK healthcare professionals. Information relating to riluzole can be accessed here.

Support

Contact details	
North, East, West Devon	Lead Clinical Nurse/Care Network Co-ordinator: Tracy Thomas Motor Neurone Disease Peninsula Network, Dept of Neurology Level 10, Derriford Hospital, Derriford Road, Plymouth PL6 8DH Telephone: 01752 436759 Or alternatively telephone the individual Trust switchboard on the numbers below and request contact with the appropriate neurology department or individual clinician: Royal Devon and Exeter NHS Foundation Trust (covering North Devon): 01392 411611 University Hospitals Plymouth NHS Trust: 01752 202082
South Devon & Torbay	Telephone: 01803 655093

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Shared Care Agreement Letter – Specialist Request

To:	**Dr:**
	Practice Address:
Patient Name:	
NHS Number:	
Date of birth:	
Address:	

Diagnosed condition: Amyotrophic lateral sclerosis form of motor neurone disease

I have discussed and agreed the following treatment with the patient: Riluzole tablets / oral suspension*

I have initiated and stabilised the patient at the following dose: 50mg every 12 hours

I request your agreement to continue the care of this patient according to the Specialised Medicines Service Guidelines for this drug. The results of any relevant baseline tests and any additional supportive information are included below and/or attached:

GPs are invited to participate, but if the GP is not confident to undertake these roles then they are under no obligation to do so. If so, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If asked to prescribe this drug the GP should reply to this request as soon as practical. Continuing the care assumes communication between the specialist, GP and patient; the intention should be explained to the patient and accepted by them.

The prescriber has the clinical and legal responsibility for the drug and the consequences of its use. Responsibility for drug monitoring and acting on results remains with the prescriber.

Specialist name:		**Date:**	
Signed:			
Telephone number:			
Email address:			

GP please sign below and return promptly. Remember to keep a copy of this letter for the patient's records. If this letter is not returned sharing of the care for this patient will not commence.

GP Response

I agree / do not agree* to share the care of this patient in accordance with the Specialised Medicines Guideline.

Signed: …….. Date: …….

GP name: ……..

*Delete as appropriate