Shared care protocol:

Riluzole for patients within adult services

As well these protocols, please ensure that summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites are reviewed for up-to-date information on any medicine.

Specialist responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision-making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see section 10) to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Assess for contraindications and cautions (see section 3) and interactions (see section 6).
- Conduct required baseline investigations and initial monitoring for at least the first 12 weeks of treatment (see section 7).
- Initiate treatment as outlined in section 4. Prescribe the maintenance treatment for at least the first 12 weeks of treatment.
- When transfer to primary care is appropriate, write to the patient's GP practice, and request shared care the shared care; detailing the diagnosis, current and ongoing dose, any relevant test results and when the next monitoring is required. Include contact information (section 12).
- Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Conduct the scheduled reviews and monitoring in section 7 and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 8 remains appropriate.

- Reassume prescribing responsibilities if a woman becomes or wishes to become pregnant.
- Provide advice to primary care on the management of adverse effects if required.
- Advise primary care if treatment should be discontinued.

Primary care responsibilities

- If shared care is not accepted, inform the specialist of the decision in writing within 14 days with reasons as to why shared care cannot be entered into.
- If accepted, prescribe ongoing treatment as detailed in the specialists request and as per section 4, taking into any account potential drug interactions in section 6. Conduct the required monitoring as outlined in section 8. Communicate any abnormal results to the specialist.
- Manage adverse effects as detailed in section 9 and discuss with specialist team when required.
- Stop riluzole if neutropenia develops. Arrange for immediate hospital assessment if neutropenic sepsis is suspected.
- Stop riluzole and make an urgent referral to the specialist if ALT rises to 5 times the ULN or if chest x-ray finding are suggestive of interstitial lung disease.
- Refer the management back to the specialist if the patient becomes or plans to become pregnant.
- Stop treatment as advised by the specialist.
- Administration of influenza and pneumococcal vaccinations as appropriate.

Patient and/or carer responsibilities

- Take riluzole as prescribed and avoid abrupt withdrawal unless advised by the prescriber.
- Attend regularly for monitoring and review appointments with primary care and specialist, and keep contact details up to date with both prescribers. Be aware that medicines may be stopped if they do not attend.
- Report adverse effects to their prescriber. Seek immediate medical attention if they develop any symptoms as detailed in section 10, particularly if signs of febrile illness.
- Report the use of any over the counter (OTC) medications to their prescriber and be aware they should discuss the use of riluzole with their pharmacist before purchasing any OTC medicines.
- Not to drive or operate heavy machinery if riluzole affects their ability to do so safely.

- Patients of childbearing potential should take a pregnancy test if they think they could be pregnant, and inform the specialist or GP immediately if they become pregnant or wish to become pregnant.

1. Background

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Riluzole is indicated for extending life or the time to mechanical ventilation for patients with the amyotrophic lateral sclerosis (ALS) variant of motor neurone disease (MND). ALS is a progressive neurodegenerative disease that causes the loss of motor neurones resulting in a gradual increase in muscle weakness and muscle wasting.

Riluzole is recommended by NICE technology appraisal guidance (TA20: Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease) as an option for treatment of people with ALS. It should be initiated by a neurological specialist with expertise in the management of MND.

Clinical trials have demonstrated that riluzole extends survival for patients with ALS, but only in the early stages of the disease. Further studies have not shown that riluzole is effective in the late stages of ALS. Patients in later stages of disease should be reviewed and given the opportunity to stop riluzole, if they consider it appropriate.

The safety and efficacy of riluzole has only been studied in ALS, therefore riluzole should not be used in any other form of MND.

Riluzole is not recommended for use in children.

2. Indications

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Licensed indication: to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

3. Contraindications and cautions

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This information does not replace the Summary of Product Characteristics (SPC), and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

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 (ULN).
- Pregnancy or breast-feeding.
- Acute porphyrias.

Cautions:

- Liver impairment: riluzole should be prescribed with care in patients with:
- a history of abnormal liver function
- slightly elevated serum transaminases (up to 3 times 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
- Interstitial lung disease has been reported in patients treated with riluzole.
- Neutropenia or febrile illness.
- Renal Impairment (due to lack of data).

4. Initiation and ongoing dose regimen

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- Transfer of monitoring and prescribing to primary care is normally after the patient has been treated for at least 12 weeks, and with satisfactory investigation results for at least 4 weeks.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
- Termination of treatment will be the responsibility of the specialist.

Usual dose:

50mg twice daily

The initial maintenance dose must be prescribed by the initiating specialist.

Conditions requiring dose adjustment:

None

5. Pharmaceutical aspects

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Route of administration:	Oral
Formulation:	50mg tablets Orodispersible 50mg film (Emylif®)- for use in exceptional circumstances following a MDT recommendation when tablets are not suitable.
Administration details:	Riluzole tablets can be crushed and dispersed in water for enteral tube administration or mixed with soft food e.g. yoghurt or puree (unlicensed). Give immediately or within 15 minutes. Ensure that the tube is flushed well after each dose. Crushed tablets may have a local anaesthetic effect in the mouth. The orodispersible films should be placed on top of the tongue; the film will stick to the tongue and begin to dissolve. Saliva should then be swallowed as the film dissolves. The films may have a local anaesthetic effect in the mouth.
Other important information:	Patients should be warned about the potential for dizziness or vertigo, and advised not to drive or operate machinery if these symptoms occur.

6. Significant medicine interactions

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The following list is not exhaustive. Please see BNF or SPC for comprehensive information and recommended management.

Riluzole is metabolised by cytochrome P450 isoform 1A2 (CYP1A2), and has the potential to interact with drugs which inhibit or induce CYP1A2. The clinical relevance of these interactions has not been established, and some of these medicines are frequently used with riluzole without incident. Discuss with specialist team if there are any concerns.

- CYP1A2 inhibitors include caffeine, diclofenac, diazepam, clomipramine, imipramine, fluvoxamine, phenacetin, theophylline, amitriptyline, quinolones, mexiletine, nicergoline, rucaparib, vemurafenib, combined hormonal contraceptives
- CYP1A2 inducers include cigarette smoke, charcoal-grilled food, rifampicin, omeprazole

7. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist

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Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care.

Baseline investigations:

- Liver function tests (LFTs), including serum transaminases, bilirubin and/or gamma-glutamyl transferase.
- Full blood count (FBC) including a differential white cell count (WCC).
- Urea and electrolytes.

Initial monitoring:

- LFTs, including alanine aminotransferase (ALT), should be measured every month during the first 3 months of treatment, every 3 months during the remainder of the first year, or until transferred to primary care.
- FBC and WCC every month during the first 3 months of treatment and every 3 months during the remainder of the first year until transferred to primary care.
- When transferring care to primary care, it should be made clear where patients are in the monitoring schedule.

Ongoing monitoring:

Routine review to assess effectiveness and ongoing appropriateness of treatment annually, or as clinically indicated.

After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 8 remains appropriate.

8. Ongoing monitoring requirements to be undertaken by primary care

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See section 9 for further guidance on management of adverse effects/responding to monitoring results.

Monitoring and advice	Frequency
• LFTs, FBC & WCC	Every month during the first 3 months of treatment, then every 3 months for the remainder of the first year. NB: where monthly or quarterly monitoring is performed in secondary care prior to transfer, there is no need to repeat individual tests. Secondary care should indicate where patients are in the monitoring schedule when transferring care. Annually after the first year.
(If relevant) If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.	

9. Adverse effects and other management

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Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

Result	Action for primary care
As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance.	
Altered LFTs Elevated LFTs up to 5 times ULN	Continue riluzole and discuss with specialist. Increase monitoring frequency if ALT is elevated.

ALT rises to 5 times ULN	Stop riluzole and inform specialist. Riluzole should not normally be re-started.
Respiratory function Dry cough or dyspnoea	Order chest x-ray. Stop riluzole immediately if findings are suggestive of interstitial lung disease. Inform specialist of findings.
Haematological parameters Febrile illness	Check WCC. Treat febrile illness according to local pathways. Arrange for immediate hospital assessment if neutropenic sepsis is suspected .
Confirmed neutropenia	Stop riluzole and inform specialist. Review patient for signs and symptoms of infection and treat or refer according to local pathways, as appropriate. Arrange for immediate hospital assessment if neutropenic sepsis is suspected.
Decreased WCC to below lower limit of local reference range	If clinical evidence of febrile illness/neutropenia, stop riluzole and treat or refer according to local pathways, as appropriate. Arrange for immediate hospital assessment if neutropenic sepsis is suspected. In the absence of febrile illness or clinical signs of neutropenia, seek advice from specialist.

10. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

- Signs or symptoms of infection, such as fever, chills or shivering, flu-like symptoms, sore throat, rashes, or mouth ulcers.
- Dry cough and/or dyspnoea.
- Signs or symptoms of liver problems, such as yellow skin or eyes (jaundice), itching all over, nausea or vomiting.

The patient should be advised:

- Not to stop taking riluzole without talking to their doctor and not to share their medicines with anyone else.
- Tell their prescriber if their smoking status changes, since this may affect their medicine
- Not to drive or operate machines if riluzole affects their ability to do so safely, e.g. by causing dizziness or drowsiness, and to inform the DVLA if their ability to drive safely is affected. See https://www.gov.uk/driving-medical-conditions and https://www.gov.uk/motor-neurone-disease-and-driving.

Patient information

- MND association riluzole information leaflet https://www.mndassociation.org/app/uploads/2015/07/5A-Riluzole.pdf
- MND Scotland riluzole fact sheet https://www.mndscotland.org.uk/media/1824/22-riluzole-2017.pdf
- NHS.uk. Low white blood cell count https://www.nhs.uk/conditions/low-white-blood-cell-count/

Patient information leaflets are also available from https://www.medicines.org.uk/emc/search?q=riluzole

11. Pregnancy, paternal exposure and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

Pregnancy:

Riluzole is contraindicated in pregnancy.

Breastfeeding:

Riluzole is contraindicated in breast-feeding women. Very limited published evidence indicates low levels in breast milk. The UK Drugs in Lactation Advisory Service recommends caution if used, and infants should be monitored for adverse effects associated with adult use.

Information for healthcare professionals: https://www.sps.nhs.uk/medicines/riluzole/

Paternal exposure:

Fertility studies in rats indicate 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. The relevance of this to human fertility is not known.

12. Specialist contact information

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The Nottingham MND Care Centre

Consultant Neurologist via secretary

MND Specialist Nurses:
Erica Littleworth 0781 226 8289 e.littleworth@nhs.net
Alyson Halliday 0115 924 9924 ext. 61792
Jo Jakupi 0781 227 0052

Out of Hours Via on call Neurology SpR at QMC

13. Additional information

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Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.

14. References

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- MND association accessed via: https://www.mndassociation.org/about-mnd/what-is-mnd/basic-facts-about-mnd/ on 20/05/21
- MND Scotland accessed via https://www.mndscotland.org.uk/ 21/05/21
- eBNF. Riluzole. Accessed via https://bnf.nice.org.uk/drug/riluzole.html 21/05/21
- NICE TA20: Guidance on the use of Riluzole (Rilutek) for the treatment of Motor Neurone Disease. January 2001. Accessed via https://www.nice.org.uk/guidance/ta20 on 21/05/21
- NICE NG42: Motor neurone disease: assessment and management. Last updated July 2019. Accessed via https://www.nice.org.uk/guidance/ng42 on 02/09/21
- Riluzole 50 mg film coated tablets (Glentek®). Date of revision of the text 29/04/2020. Accessed via https://www.medicines.org.uk/emc/product/10060/smpc on 21/05/21
- Riluzole 50 mg film-coated tablets (Rilutek®) Date of revision of the text 01/01/2021. Accessed via https://www.medicines.org.uk/emc/product/1101/smpc on 21/05/21
- Riluzole 50 mg film-coated tablets (Ranbaxy UK Ltd). Date of revision of the text 15/02/2018. Accessed via https://www.medicines.org.uk/emc/product/5185/smpc on 21/05/21
- Riluzole 50mg Film-Coated Tablet (Accord-UK Ltd). Date of revision of the text 18/07/2019. Accessed via https://www.medicines.org.uk/emc/product/2831/smpc on 21/05/21

- Riluzole 5 mg/ml oral suspension (Teglutik®). Date of revision of the text 10/11/2019. Accessed via https://www.medicines.org.uk/emc/product/5060/smpc on 21/05/21
- Handbook of Drug Administration via Enteral Feeding Tubes. Riluzole. Last updated 15/02/18. Accessed via https://www.medicinescomplete.com/#/content/tubes/c330 on 20/05/21
- NEWT Guidelines. Riluzole. Last updated October 2020. Accessed via https://access.newtguidelines.com/R/Riluzole.html on 20/05/21
- Specialist Pharmacy Service. Riluzole Lactation Safety Information. Last updated 3 August 2020. Accessed via https://www.sps.nhs.uk/medicines/riluzole/ on 10/06/21
- NICE Clinical Knowledge Summaries. Neutropenic sepsis: management. Last revised March 2020. Accessed via https://cks.nice.org.uk/topics/neutropenic-sepsis/management/management/ on 11/06/21

15. Other relevant national guidance

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- Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/
- NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/

16. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

- The request for shared care should be accompanied by individual patient information, outlining all relevant aspects of the patient's care and which includes direction to the shared care protocols on the APC website.
- The specialist will request shared care with the GP in writing.
- If the GP doesn't agree to shared care, they should inform the specialist of their decision in writing within 14 days, outlining the reason for the decline. The agreement can be assumed if the GP does not provide a written decline.

- In cases where shared care arrangements are not in place or where problems have arisen within the agreement, and patient care may be affected, the responsibility for the patient's management, including prescribing, reverts back to the specialist.
- Should the patient's condition change, the GP should contact the relevant specialist using the details provided with the shared care request letter.