



*National Institute for
Clinical Excellence*

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Guidance on
the Use of
Riluzole
(Rilutek) for the
Treatment of
Motor Neurone
Disease

This document has been circulated to the following:

- Health Authority Chief Executives in England and Wales
- NHS Trust Chief Executives in England and Wales
- PCG Chief Executives
- Local Health Group General Managers
- Medical and Nursing Directors
- All GP partners in England and Wales
- Consultant Neurologists in England and Wales
- Chief Pharmacists, Heads of Drug Purchasing, Heads of Drug Information, Pharmaceutical Advisors, GP Prescribing Advisors and Purchase Advisors in England and Wales
- NHS Director Wales
- Chief Executive of the NHS in England
- NHS Executive Regional Directors
- Special Health Authority Chief Executives
- Community Health Councils in England and Wales
- Patient advocacy groups
- Commission for Health Improvement
- NHS Clinical Governance Support Team
- Chief Medical and Nursing Officers in England and Wales
- Medical Director & Head of NHS Quality – National Assembly for Wales
- Clinical Effectiveness Support Unit - Wales
- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

This Guidance is written in the following context:

This guidance represents the view of the Institute's Appraisal Committee, the membership of which is set out in Appendix A, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgment about the use of riluzole in the treatment of Motor Neurone Disease. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Guidance on the Use of Riluzole (Rilutek) for the Treatment of Motor Neurone Disease

1. Guidance

- 1.1 Riluzole is recommended for the treatment of individuals with the amyotrophic lateral sclerosis (ALS) form of Motor Neurone Disease (MND).
- 1.2 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.

This section (Section 1) constitutes the Institute's Guidance on the use of riluzole for Motor Neurone Disease. The remainder of the document is structured in the following way:

2	Clinical Need	8	Clinical Audit Advice
3	The Technology	9	Review of Guidance
4	Evidence	Appendix A:	Appraisal Committee
5	Implications for the NHS	Appendix B:	Sources of Evidence
6	Further Research	Appendix C:	Information for Patients.
7	Implementation		

The full document and a Summary of Evidence are available from our website at www.nice.org.uk or by telephoning 0541 555 455 and quoting the reference number 23071.

Mae'r adran hon (adran 1) hefyd ar gael yn Gymraeg ar ein gwefan neu drwy gysylltu â 0541 555 455, rhif cyfeirnod 23072.

Technology Appraisal Guidance No. 20

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- 2.1 Motor neurone disease (MND) is characterised by progressive degeneration of the motor neurones of the brain, brain stem or spinal cord. Depending on the site of the lesions, characteristic signs may include spasticity, muscle stiffness, brisk or diminished reflexes, muscle wasting and fasciculation, and both flaccid and/or spastic weakness.
- 2.2 The classification and terminology used to describe the different Motor Neurone Disease syndromes are not always clear or consistent. This partly reflects uncertainties surrounding the underlying causes of MND and the mechanism of neuronal damage. There is also debate about the extent to which different syndromes are simply manifestations of the same disease process or whether there are several different disease mechanisms.
- 2.3 The term 'Motor Neurone Disease' is used to describe variants of the disease – namely progressive muscular atrophy (PMA) and amyotrophic lateral sclerosis (ALS) which includes Progressive Bulbar Palsy (PBP). ALS, which is characterised by both upper and lower motor neurone signs, is the most common form of MND, accounting for 65% to 85% of all cases. Adult-onset MND usually starts insidiously with symptoms and signs including stumbling, foot drop, weakened grip, slurred speech, cramp, muscle wasting, twitching and tiredness. Other symptoms of MND include muscle stiffness, paralysis, in-coordination and impaired speech, swallowing and breathing. Most individuals die from ventilatory failure, resulting from progressive weakness and wasting of limb, respiratory and bulbar muscles within approximately 3 years of the onset of symptoms.
- 2.4 The Institute was advised that, despite the terms of the product licence, it has been common clinical practice for riluzole to be used in all of the forms of MND referred to in paragraph 2.3. This may in part be because the mainland European and UK nomenclature for the disease differs. In mainland Europe, the terms MND and ALS are often used interchangeably. This document refers to ALS specifically in accordance with the terminology used in the current product licence for riluzole.
- 2.5 There is no diagnostic test for MND. The diagnosis requires the demonstration of clinical signs affecting both the brain and spinal cord. Diagnosis is often delayed and can take more than 16 months from the onset of initial symptoms, which are commonly non-specific and include general fatigue.
- 2.6 The incidence of ALS ranges from 1.8 to 2.2 per 100,000 population and prevalence ranges from 4.0 to 4.7 per 100,000 population in UK. Therefore at any one time about 2000 individuals per year in England and Wales are affected by ALS.
- 2.7 There is a range of pharmacological interventions that provide symptomatic relief for people with MND. Surgical intervention may be necessary. Such interventions include

percutaneous gastrostomy to enable feeding as the ability to swallow decreases and tracheostomy with or without ventilatory support to aid breathing as respiratory muscle weakness increases.

2.8 Supportive and palliative care is currently available for people with MND. A wide range of multidisciplinary health and social services is required, particularly in the late stages of the disease, and need to be tailored to suit individual needs. NHS, personal social service and voluntary sector services needed include physiotherapy, occupational therapy, speech and language therapy and augmentative communication, mobility aids and district nursing support. In the later stages of the disease, the following interventions may also be required: enteral feeding (for severe dysphagia), domiciliary or hospice care, and ventilatory support, including mechanical ventilation and tracheostomy.

3

The Technology

3.1 Riluzole (Rilutek) is currently the only drug licensed for treating ALS in the UK. The licensed indication of riluzole is to extend life or the time to mechanical ventilation for individuals with ALS. The Summary of Product Characteristics (SPC) recommends that riluzole should not be used in any other form of Motor Neurone Disease. The SPC also suggests that treatment should only be initiated by specialist physicians with experience in the management of Motor Neurone Disease.

3.2 It is hypothesised that excessive stimulation of glutamate receptors on neurones may cause or play an important role in the destruction of motor neurones in MND. Glutamate is a neurotransmitter that tends to excite motor neurone cells. In vitro, riluzole inhibits the release of glutamate; decreases firing of motor neurones induced by glutamate receptor agonists and thus protects cells from glutamate-mediated damage.

3.3 The main caution for use of riluzole is history of abnormal hepatic function. Regular blood testing (every month for 3 months, then every 3 months for a further 9 months and annually thereafter) is recommended to monitor hepatic function. Side effects include nausea, vomiting, weakness, tachycardia, somnolence, headache, dizziness, vertigo, pain, paraesthesia and alterations in liver function tests. Side effects of dizziness or vertigo may affect the performance of skilled tasks such as driving. Riluzole is contraindicated in the presence of hepatic and/or renal impairment and during pregnancy and breast-feeding.

3.4 The license dosage of riluzole is 100mg per day (50mg twice per day). The NHS list price (excluding VAT) of riluzole is £286 per treatment course, which amounts to an annual cost of £3718. An additional cost, incurred for monitoring liver enzymes, has been estimated to be a maximum of £24 per year, giving a total annual cost of treatment with riluzole of £3742.

- 4.1 Four randomised controlled trials (including a number of UK centres) in patients who fall within the diagnostic category of ALS have compared riluzole with placebo (a total of 1477 individuals). Three trials used riluzole at 100 mg/day and one used doses of 50, 100 and 200mg/day. Individuals were under 75 years, had a Forced Vital Capacity (FVC) $\geq 60\%$ in three trials, with two of these also excluding patients who had suffered from MND for more than 5 years. The fourth trial recruited individuals who were older or who had a greater duration of disease (> 5 years) or who had a FVC $<60\%$.
- 4.2 All trials used tracheostomy-free survival as a primary outcome. Most individuals (in all four trials) were prevalent, rather than incident cases.
- 4.3 The assessment report reviewed the results from all four of the trials identified and reported riluzole to be associated with a relative reduction in hazard ratio for tracheostomy-free survival at 18 months of 17% (i.e. hazard ratio of 0.88, 95% CI: 0.75-1.02). There was some evidence of heterogeneity across the results of these four trials.
- 4.4 When data on functional status were combined, a small reduction in the rate of deterioration of functional status was observed, although the statistical methods used to calculate changes were questionable. Furthermore it is not clear whether the estimated differences obtained using these methods were clinically significant.
- 4.5 There was little evidence of a difference in adverse events between riluzole and placebo.
- 4.6 There is strong clinical support for the use of riluzole in forms of MND other than ALS but the current licensed indications limit its use to ALS alone. The inclusion criteria for the published clinical trials has been restricted to a diagnosis of the ALS form of MND alone.
- 4.7 Current estimates of the cost-effectiveness of riluzole must be viewed cautiously. Some of the key remaining uncertainties on benefits for the economic analysis concern the disease stage(s) in which the survival gain is experienced, the quality of life utility weights for ALS health states and the mean gain in life expectancy for individuals who take riluzole. Estimates from the two fully published trials suggest a gain in median tracheostomy free survival time of 2 months to 4 months. It is clear that riluzole is associated with a net increase in costs to the health service, though the magnitude of the increase is difficult to predict accurately.

- 4.8 Using a published Markov model and 18 month trial follow up data, the manufacturer's submission provided a base case cost per quality adjusted life year (cost/QALY) estimate of £18,000 to £29,000 for riluzole. Based on a re-analysis of this Markov model using an alternative, more conservative, estimate of time-dependant probabilities, the assessment report derived discounted cost per QALY estimates for riluzole of between approximately £34,000 to £43, 500. These later estimates are consistent with the results obtained by the assessment report authors when using Weibull and Gompertz models to extrapolate survival over time.
- 4.9 The Appraisal Committee considered the evidence of the clinical and cost effectiveness of this technology by reference to the Directions to the Institute issued by the Secretary of State. The Committee took account of the severity and relatively short life span of people with ALS and in particular, as directly reported to it, of the values which patients place on the extension of tracheostomy free survival time. With these considerations in mind, the Committee considered that the net increase in cost for the NHS of the use of riluzole in this indication was reasonable when set against the benefit, assessed as extended months of an acceptable (to patients) quality of life.
- 4.10 The documentation and opinion available to the Appraisals Committee is set out in Appendix B.

5

Implications for the NHS

- 5.1 It is estimated that the potential budget impact to the NHS in the England and Wales of making riluzole available to all individuals with ALS would be at maximum around £7.5 million per annum. Given an estimated current level of funding of riluzole for ALS of about £2 million per annum, this represents an additional cost to the NHS in England and Wales of about £5 million. However, there is considerable uncertainty about the proportion of patients who will take up this therapy. Moreover, these figures do not take into account the additional NHS costs of patient survival.
- 5.2 A diagnosis of MND should be made or confirmed by a specialist physician with experience in the management of Motor Neurone Disease after appropriate investigations. 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.
- 5.3 In the latter stages of their disease, patients may wish to review their continued use of riluzole and they should be provided with the opportunity to discontinue treatment, if after discussion with the responsible clinician, they consider it appropriate.

6

Further Research

- 6.1 Further trials of riluzole are required to examine the relative effectiveness of differing dosing regimens.
- 6.2 Methods for the early diagnosis of MND require development as they may enable earlier treatment and enhanced clinical outcomes.

7

Implementation

- 7.1 NHS trusts with responsibility for treating people with Motor Neurone Disease should enable neurologists to consider the option of using riluzole in the way set out in Section 1.
- 7.2 Neurologists with responsibility for patients with MND should review their current practice in line with the guidance set out in Section 1.
- 7.3 The patient information attached to this guidance as Appendix C can be drafted into local information leaflets as advice for people with MND and those who care for them.

8

Clinical Audit Advice

- 8.1 To enable clinicians to audit their own compliance with this guidance it is recommended that treatment plans are recorded for each patient.
- 8.2 This information should be incorporated into local audit data recording systems and consideration given (if not already in place) to the establishment of appropriate categories in routine electronic record keeping systems used in hospitals and the multi-disciplinary groups working in support of people with MND.
- 8.3 Relevant clinical guidelines and protocols linking the multi disciplinary working for people with MND should be reviewed in the light of this guidance.
- 8.4 Prospective clinical audit programmes should record the proportion of treatments adhering to this guidance. Such programmes are likely to be more effective in improving patient care when they form part of the organisation's formal clinical governance arrangements and where they are linked to specific post-graduate activities.

9

Review of Guidance

- 9.1 This advice will be reviewed in the light of new evidence in January 2004.

Andrew Dillon
Chief Executive
January 2001

APPENDIX A

Appraisal Committee Members

The Appraisal Committee is a Statutory Committee whose members sit for 3 years. They are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L.Akehrst
Dean, School of Health Related
Research
Sheffield University

**Professor David Barnett
(Chairman)**
Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy
St Bartholomew's and Royal London
School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Professor Martin Buxton
Director of Health Economics
Research Group
Brunel University

Professor Yvonne Carter
Professor of General Practice and
Primary Care
St Bartholomew's and Royal London
School of Medicine

Dr Karl Claxton
Lecturer in Economics
University of York

Professor Duncan Colin-Jones
Professor of Gastroenterology
University of Southampton

Professor Sarah Cowley
Professor of Community Practice
Development
Kings College, London

Dr Nicky Cullum
Reader in Health Studies
University of York

Mr Chris Evennett
Chief Executive
Mid-Hampshire Primary Care Group

Professor Terry Feest
Clinical Director and
Consultant Nephrologist
Southend Hospital

Ms Jean Gaffin
Formerly Executive Director
National Council for Hospice and
Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive
Merton, Sutton and Wandsworth
Health Authority

Dr Trevor Gibbs
International Medical Operations
Director
Glaxo-Wellcome R&D Ltd

Mr John Goulston
Director of Finance
The Royal Free Hampstead NHS
Trust

Professor Philip Home
Professor of Diabetes Medicine
University of Newcastle

Dr Terry John
General Practitioner
The Firs, London

Dr Diane Ketley
Clinical Governance Programme
Leader
Leicester Royal Infirmary

Dr Mayur Lakhani
General Practitioner, Highgate
Surgery, Leicester and
Lecturer, University of Leicester

Mr M Mughal
Consultant Surgeon
Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive
Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales

Professor Andrew Stevens
Professor of Public Health
University of Birmingham

APPENDIX B

Sources of Evidence

1. The following documentation and opinion was made available to the Committee:
 - a. Assessment Report
 - Assessment report '*The clinical effectiveness and cost effectiveness of Riluzole in the Treatment of Motor Neurone Disease*' by Stewart, Sandercock, Bryan, Hyde, Fry-Smith, Burls. West Midlands Development & Evaluation Service, University of Birmingham
 - Update Assessment Report prepared by the West Midlands Development and Evaluation Service (The clinical effectiveness and cost-effectiveness of Riluzole for Motor Neurone Disease, August 2000)
 - b. Manufacturer/Sponsor submissions:
 - Aventis Pharma
 - c. Professional/Specialist Group, Patient/Carer Group and Trade Association submissions:
 - Association of British Neurologists & Royal College of Physicians
 - Association for Palliative Medicine of Great Britain and Ireland
 - Chartered Society of Physiotherapy
 - Motor Neurone Disease Association
 - Royal College of General Practitioners
 - Royal College of Nursing
 - Royal College of Speech and Language Therapists
 - d. External expert and patient advocate submissions:
 - Professor Pamela Shaw, Section of Neurology, Royal Hallamshire Hospital, Sheffield
 - Ms. Julia Johnson, Speech and Language Therapist, King's College Hospital
 - Mr. George Levvy, Chief Executive, MND Association
 - Mr. Chris Davies, Member of MND Association

APPENDIX C

Guidance on the use of Riluzole (Rilutek) for the Treatment of Motor Neurone Disease – patient information

The patient information in this appendix has been designed to support the production of your own information leaflets; you can download it from our web site (www.nice.org.uk) where it is available in English and Welsh. A printed version of this text is available in English/Welsh or English alone. If you would like copies of the printed leaflet please contact 0541 555 455, and quote the reference number 23072 for the English/Welsh version and 23073 for the English only version.

What is NICE Guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment, diagnostic tests and clinical & surgical procedures and where they should be used.

When the Institute evaluates these things, it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, the professional organisations and the groups who represent patients.

NICE was asked to look at the available evidence on riluzole (Rilutek) and provide guidance that would help the NHS in England and Wales decide where it should be used in the treatment of Motor Neurone Disease.

What is Motor Neurone Disease?

Motor Neurone Disease (MND) is the name given to a group of diseases that affect the motor neurones in the brain and spinal cord. Motor neurones are the nerve cells along which the brain sends instructions, in the form of electrical impulses, to the muscles.

Deterioration of these cells leads to weakness and wasting of muscles. In the majority of cases the symptoms first occur in the arms and legs. Some people may develop weakness and wasting in the muscles supplying the face and throat, causing problems with speech and difficulty chewing and swallowing.

MND does not affect touch, taste, sight, smell or hearing, nor directly bladder, bowel, or sexual function. In the vast majority of cases, the intellect remains unaffected.

MND is generally a progressive disease and the rate of progression can vary greatly from one person to another.

Amyotrophic lateral sclerosis (ALS) is the most common form of MND, accounting for up to 8 out of 10 of all cases.

People with MND do not get better and most people with MND die within approximately 3 years of the onset of symptoms. Most people with MND eventually pass through a phase which is characteristic of ALS.

What is riluzole (Rilutek)?

Riluzole (Rilutek) is a medicine that can be used to treat some forms of Motor Neurone Disease. Although it is not a cure, research has shown that it can prolong survival. The prescription of riluzole should only be started by a specialist who has experience in the management of MND.

What has NICE recommended about the use of riluzole?

NICE has recommended to the NHS that riluzole should be available for the treatment of individuals with MND in accordance with its licensed indications.

Treatment with riluzole should only be started by a neurological specialist who is experienced in the management of MND. Routine supervision of therapy may be managed by general practitioners, but this should be under an agreement known as a shared care arrangement with the specialist.

What should I do?

If you, or someone you care for has Motor Neurone Disease, you might want to discuss this guidance with your GP or neurologist. If you have access to the Internet and would like to find out more about MND visit the NHS Direct website (www.nhsdirect.nhs.uk) and search for Motor Neurone Disease.

Will NICE review its Guidance?

Yes. The guidance will be reviewed in January 2004.

Further Information

Further information on NICE, and the full guidance issued to the NHS is available on the NICE web site (www.nice.org.uk). It can also be requested from 0541 555 455, quoting reference 23071.