

Shared Care Guideline Rufinamide

Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients aged 16 years and over

Dear GP,

The information in the shared care guideline has been developed in consultation with Primary Care and it has been agreed that it is suitable for shared care.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the Consultant when treatment is initiated. It is important that patients are consulted about treatment and are in agreement with it.

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of Rufinamide (Inovelon[®]) for patients over the age of 16 with Lennox-Gastaut Syndrome (LGS) refractory to standard treatments can be shared between the specialist (i.e. neurologist), the patient and yourselves as the patient's general practitioner (GP).

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1. Introduction

This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing rufinamide.

LGS is a rare epilepsy syndrome of paediatric origin. It is characterised by a triad of slow spike-and-wave pattern on EEG, multiple types of seizures (tonic, atypical absence, drop attacks) occurring at a high daily frequency, and impaired mental development. Despite the availability of numerous antiepileptic drugs (AEDs) approximately 30% of patients with epilepsy are refractory to current medication; however, in patients with LGS, despite the use of multiple AEDs, seizures persist in more than 75% of cases.

Rufinamide is structurally distinct from other currently available AEDs. Rufinamide reduces the capacity of neuronal sodium channels to recover from inactivation, thus prolonging their inactive state. It limits neuronal sodium-dependant action potential firing, mediating anticonvulsant effects.

Once a stable, optimal dose of rufinamide has been achieved by the patients consultant, a shared care arrangement with you will be requested. It will clarify responsibilities between the specialist and general practitioner (GP) for managing the prescribing of rufinamide such as:

- Who will prescribe;
- Who will monitor;
- Specific clinical monitoring is not routinely required in patients taking rufinamide. If there is an exception to this, the prescribing consultant must specify the test(s) that are required, why they are needed, the frequency of testing and the location of testing and actions to be taken in the case of an abnormal result(s)
- Which clinician will be responsible for receipt and review of the results;
- Who will communicate any necessary changes in dose to the patient and the GP.

2. Shared Care criteria

Patients who are stabilised on rufinamide and have been monitored appropriately at baseline and after initiation of treatment with no problems identified during this period.

3. Shared care responsibilities

3.1. Consultant Neurologist

Send a letter to the GP along with shared care criteria and transfer form (see Appendix 1) requesting shared care for this patient. The indication, dose and frequency is to be decided by the hospital team.

- 1) Discuss the benefits and side effects of treatment with the patient. Provide the patient with a Patient Information Leaflet where possible and ensure that the patient understands the reason for the treatment and dosing regimen
- 2) Decide with the patient how they will document their seizure type and frequency. This may be by providing a seizure diary to the patient or agreeing for the patient to document this information in their own diary or electronic device
- 3) Initiate treatment and prescribe until the GP formally agrees to share care (until patient is stabilised or as according to Section C for local minimum supply durations). Patients will be seen in clinic prior to consideration of shared care
- 4) Counsel the patient on potential adverse effects to monitor (e.g. very common adverse events such as somnolence, headache, dizziness, nausea, vomiting and fatigue), and should be informed to seek medical advice if any signs of suicidal ideation or behaviour emerge (see 5: Adverse effects).
- 5) Discuss the shared care arrangement with the patient
- 6) Provide results of any baseline tests that have been performed. The SPC for rufinamide does not specify that routine clinical monitoring is required in patients taking rufinamide. However, if the consultant deems any tests to be performed, the consultant must state what the recommended tests are, why they are needed and the location in which these tests will be carried out
- 7) Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated
- 8) Inform GP of blood test results, actions to take in case of abnormal results, and advise the GP on when to adjust the dose, stop treatment, or consult with specialist
- 9) Periodically review the patient's condition and communicate promptly with the GP when treatment is changed. Counsel the patient on any dose changes that are made during clinic appointments
- 10) Evaluate adverse effects reported by GP or patient
- 11) Report adverse events to the MHRA (via yellow card scheme) and GP
- 12) Inform GP of patients who do not attend clinic appointments
- 13) Ensure that clear backup arrangements exist for GPs to obtain advice and support

3.2. General Practitioner

Complete transfer form and send back to *hospital* confirming acceptance/ rejection of shared care for patient. If GP unable to agree to shared care, inform the Hospital team stating reasons within **14 days** of receipt of request. If no response is received within 14 days, the Consultant will assume the GP has accepted shared care.

- 1) Monitor patient's overall health and well-being
- 2) Prescribe the drug treatment as described (but not to alter the dose unless advised to do so by the specialist). The term "as directed" **SHOULD NOT** be used
- 3) Ensure that the patient understands the dosing
- 4) Ensure the patient understands that he/she must report the warning symptoms as listed under "adverse effects"
- 5) Ensure compatibility with concomitant medication
- 6) Monitor results at recommended frequencies as described under "clinical monitoring" and inform the Consultant if abnormal
- 7) Adjust the dose as advised by the specialist (where applicable) and counsel patient on any dose changes
- 8) Report any adverse events and non-compliance to the hospital specialist, where appropriate
- 9) Stop treatment on advice of specialist or immediately if urgent need arises
- 10) Help monitor disease progression and inform the hospital team of any changes to medication
- 11) Report adverse events to the specialist and MHRA via the yellow card scheme
- 12) All requests for repeat prescriptions should be reviewed individually prior to issuing

3.3. Patient responsibility

- 1) Attend all hospital and GP appointments
- 2) Monitor seizure activity as agreed with consultant
- 3) Take medicines as agreed
- 4) Report to the consultant neurologist, epilepsy nurse specialist or GP if he/she does not have a clear understanding of the treatment
- 5) Inform specialist or GP of any other medication being taken, including over-the-counter products
- 6) Report any adverse effects or warning symptoms to GP or specialist immediately
- 7) Inform hospital and GP of any changes in address or telephone numbers

3.4. Clinical Commissioning Group

- 1) To provide feedback to Trusts from the standard letter, via the shared care forum.
- 2) To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
- 3) To support Trusts in the resolving issues that may arise as a result of shared care.

4. Indications, dose and administration

Rufinamide is indicated as adjunctive therapy in the treatment of seizures associated with LGS in patients aged 1 year and over.

First-line treatment options on the NCL Joint Formulary for LGS include sodium valproate, lamotrigine, carbamazepine and oxcarbazepine. Second-line options include topiramate, clobazam, clonazepam, ethosuximide and levetiracetam.

Rufinamide has been agreed as a third-line treatment option in patients with LGS who have failed treatment with or are intolerant to alternative agents. Initiation of rufinamide is restricted to Consultant epileptologists.

Rufinamide should be taken twice a day with food.

Rufinamide may be administered with **or** without sodium valproate and this can alter the dose of rufinamide prescribed for a patient.

Patients weighing > 30kg and also receiving sodium valproate:

Treatment should be initiated at a dose of 400mg daily (administered as 200mg twice daily). This can be increased depending on clinical response and tolerability in 400mg/day increments as frequently as every other day up to a maximum recommended dose as indicated in the table below:

Patient weight range	Maximum daily dose
30.0 - 50.0 kg	1200mg/day
50.1 – 70.0 kg	1600mg/day
≥ 70.1 kg	2200mg/day

Patients weighing > 30kg and NOT receiving sodium valproate

Treatment should be initiated at a daily dose of 400 mg (administered as 200mg twice daily). According to clinical response and tolerability, the dose may be increased by 400 mg/day increments, as frequently as every other day, up to a maximum recommended dose as indicated in the table below.

Patient weight range	Maximum daily dose
30.0 - 50.0 kg	1800mg/day
50.1 – 70.0 kg	2400mg/day
≥ 70.1 kg	3200mg/day

If the recommended calculated dose of rufinamide is not achievable, the dose should be rounded to the nearest whole 100mg tablet.

Elderly

Since the pharmacokinetics of rufinamide are not altered in older people, dosage adjustment is **not** required in patients > 65 years of age.

Renal and hepatic impairment

No dose adjustments are required for patients with severe renal impairment.

Caution and careful dose titration is recommended when treating patients with mild to moderate hepatic impairment and use in severe hepatic impairment is not recommended. Liver impairment is graded by how high liver functions tests (LFTs) are over the upper limit of normal (ULN):

Severe hepatic impairment: 5x or more ULN of LFT markers

Moderate hepatic impairment: ≥3x to <5x ULN of LFT markers

Mild hepatic impairment: ≥ULN to <3x the upper limit of normal of LFT markers

Discontinuation of rufinamide

When treatment is to be discontinued, it should be withdrawn gradually and this should be guided by the consultant. In clinical trials, rufinamide discontinuation was achieved by reducing the dose by approximately 25% every two days.

In the case of one or more missed doses, individualised clinical judgement is necessary.

Preparations available

Tablets for oral administration: 100mg, 200mg and 400mg film-coated tablets.

For patients that have difficulty swallowing, tablets can be crushed and administered in half a glass of water. Alternatively, use the score line to break the tablet into two equal halves for administration.

Oral suspension: 40mg/1ml (460ml total volume)

The manufacturer advises that rufinamide (Inovelon) oral suspension and rufinamide (Inovelon) film-coated tablets may be interchanged at equal doses. Care should be taken when switching between formulations and the patient should be monitored during the switch over period.

5. Adverse effects

The most commonly reported adverse reactions overall for patients with different types of epilepsy exposed to rufinamide were headache, dizziness, fatigue, and somnolence. The most common adverse reactions observed at a higher incidence than placebo in patients with LGS were somnolence and vomiting.

The discontinuation rate in LGS due to adverse reactions was 8.2% for patients receiving rufinamide and 0% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from the rufinamide treatment group were rash and vomiting.

Very common ($\geq 1/10$) adverse effects include:

- Somnolence, headache, dizziness, nausea, vomiting and fatigue.

Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the CHM.

There has been reports of suicidal ideation and behaviour with antiepileptic agents in several indications. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Inovelon. Patients should be monitored for signs of suicidal ideation & behaviour, and should be advised to seek medical advice if signs emerge during treatment.

6. Cautions

- Status epilepticus cases have been observed during treatment with rufinamide in clinical development studies, whereas no such cases were observed with placebo. If patients develop new seizure types and/or experience an increased frequency of status epilepticus that is different from the patient's baseline condition, then the benefit-risk ratio of the therapy should be reassessed.
- As rufinamide treatment has been associated with dizziness, somnolence, ataxia and gait disturbances, this has the potential to increase the occurrence of accidental falls in this population. Patients and carers should exercise caution as a result of these potential side-effects.
- Inovelon tablets contain lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- At time of writing no clinical data on exposed pregnancies to rufinamide are available. As a result, women of childbearing potential must use contraceptive measures during treatment with rufinamide. Physicians should try to ensure that appropriate contraception is used and if treated women plan to become pregnant, the continued use of the product should be carefully weighed by the patients specialist.
- Serious antiepileptic medicinal product hypersensitivity syndrome including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and Steven-Johnson Syndrome have occurred in combination with rufinamide therapy. Signs and symptoms of these reactions are diverse and include fever, rashes, lymphadenopathy, LFT abnormalities and haematuria. The hypersensitivity syndrome occurred in close association to the initiation of rufinamide therapy and in the paediatric population. Rufinamide is to be discontinued and alternative treatments started if this reaction is suspected. All patients who develop a rash whilst taking rufinamide must be closely monitored.
- In an MHRA alert regarding advice on switching between different manufacturers products for a particular antiepileptic drug, rufinamide was considered a category 2 risk; that is, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history.⁵ Therefore, GPs and Community Pharmacists should ensure the patient is maintained on one manufacturers product unless a clinical decision has been made and documented.

This is not an exhaustive list of cautions. For a full list, please refer to the Summary of Product Characteristics.

7. Clinical Monitoring

The manufacturer of Inovelon tablets and liquid does **not** specify that routine clinical monitoring is required in patients treated with rufinamide.

As per section 3.1, patients should continue to keep a seizure diary and any possible adverse events should be reported promptly to the GP and Consultant neurologist.

If additional tests are recommended, the consultant should explain what these tests are and the rationale for doing them in addition to the location for the tests to be carried out. The consultant should detail who is to review the results and the action(s) to be taken if a result is abnormal.

At each review, the patient should be monitored for signs of suicidal ideation and behaviour (possibility of an increased risk with Inovelon), and appropriate treatment considered.

8. Contraindications

- Hypersensitivity to the active substance, triazole derivatives or to any of the excipients
- Inovelon **tablets** contain lactose therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take tablets. The oral solution can be used safely in this group of patients.

For a full list of **excipients**, refer to the Summary of Product Characteristics.

9. Drug Interactions

Rufinamide and other antiepileptic medicinal products

In pharmacokinetic studies, rufinamide does **not** appear to have a clinically relevant effect on carbamazepine, lamotrigine, phenobarbital, topiramate, phenytoin or valproate steady state concentrations.

For patients taking rufinamide who have sodium valproate initiated, significant increases in rufinamide plasma concentrations may occur. As a result, consideration should be given to a dose reduction of rufinamide with concomitant valproate therapy.

No significant changes in rufinamide concentrations are observed following co-administration with lamotrigine, topiramate or benzodiazepines.

Oral contraceptives

Rufinamide co-administered with a combined oral contraceptive (ethinylestradiol and norethindrone) resulted in a mean decrease in plasma concentrations of the contraceptive. Studies with other oral or implant contraceptives have not been conducted.

Women of child-bearing potential using hormonal contraceptives are advised to use an additional safe and effective contraceptive method.

Cytochrome P450 enzymes

Rufinamide is metabolised by hydrolysis and is not metabolised to any notable degree by cytochrome P450 enzymes. Furthermore, it does not inhibit the activity of CP450 enzymes.

Rufinamide has been shown to induce the cytochrome P450 enzyme CYP3A4 and may therefore reduce the plasma concentrations of substances which are metabolised by this enzyme.

It is recommended that patients treated with substances that are metabolised by the CYP3A4 enzyme system are to be carefully monitored for two weeks at the start of, or after the end of treatment with rufinamide, or after any marked change in the dose. A dose adjustment of the concomitantly administered medicinal product may need to be considered. These recommendations should also be considered when rufinamide is used concomitantly with substances with a narrow therapeutic window such as warfarin and digoxin.

No data on the interaction of rufinamide with alcohol are available.

For further information regarding these drug interactions or for specific information regarding drug-drug interactions, refer to the Manufacturers Summary of Product Characteristics or the most up to date version of Stockleys' Drug Interactions.

10. References

Provide an up-to-date evidence base for procedural documents using Vancouver style. Websites should include hyperlinks and 'date last accessed', SPCs should include title in full, manufacturer and date last updated on eMC.

1. Summary of Product Characteristics for Inovelon[®] tablets. Eisai Limited. Accessed online via: <https://www.medicines.org.uk/emc/product/410/smpc> on 30/4/19
2. Summary of Product Characteristics for Inovelon oral suspension. Eisai Limited. Accessed online via: <https://www.medicines.org.uk/emc/product/2354/smpc> on 30/4/19
3. British National Formulary 2018/19. Edition 76 . Accessed online via www.medicinescomplete.com on 30/4/19
4. UCLH online formulary 2019
5. Antiepileptic drugs: new advice on switching between different manufacturers' products for a particular drug. Medicines and Healthcare products Regulatory Agency. Accessed online via <https://www.gov.uk/drug-safety-update/antiepileptic-drugs-new-advice-on-switching-between-different-manufacturers-products-for-a-particular-drug> on 16/09/2019.

11. Contact Details

National Hospital for Neurology and Neurosurgery (NHNN)

Hospital switchboard:	020 3456 7890
Epilepsy specialist nurses advice line and email address	020 3448 8627 (answerphone) uclh.epilepsy@nhs.net
Specialist or Dept. Pharmacist: NHNN Pharmacist	020 3448 3277
Consultant details:	Please contact the relevant consultants secretary via the UCLH hospital switchboard (telephone number above)

Document management

Groups / Individuals who have overseen the development of this guidance:	Sofia Eriksson, NHNN Sheetal Sumaria, NHNN Jaspreet Girn, NHNN NCL JFC Support Pharmacists
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Appendix 1: Shared care transfer form: from UCLH to GP practice

Section A: to be completed by secondary care *Send to GP practice*

This document is to request the shared care pathway of your patient and comprises an agreement between the GP and named consultant. The patient will continue to be seen by the named consultant as regular follow up.

<i>Fix address label here (ensure NHS no. on)</i>		<i>Clinic stamp or give details below</i>	
Department	<input type="text"/>		
Clinic phone (remove)	<input type="text"/>		
Consultant	<input type="text"/>	Email	<input type="text"/>
Indication for prescription	<input type="text"/>		
Drug prescribed	<input type="text"/>		
Date	Drug started <input type="text"/>	Current dose	<input type="text"/>
Relevant conditions	<input type="text"/>		
Monitoring variations	<input type="text"/>		
Date next blood test	<input type="text"/>	Next disease review due in	<input type="text"/> months' time.

Section B: [Accept Shared Care] to be completed by practice *Send back FAO referring consultant above*

The above patient has been accepted into our monitoring service.

Practice date for next blood test	<input type="text"/>	Practice stamp
Signed / Designation	<input type="text"/>	
Date	<input type="text"/>	

Section B: [Reject Shared Care] to be completed by practice *Send back FAO referring consultant above*

The above patient has not been accepted into our monitoring service.

Reason	<input type="text"/>	Practice stamp
Signed / Designation	<input type="text"/>	
Date	<input type="text"/>	

Section C: Shared Care Agreement (Trust specific information)

This section (and reference to it: Consultant Shared Care Responsibilities point 3) can be removed if all Trusts and CCGs have the same contractual arrangements.

Contact details	
Clinic / service	
Address	
Email	
Telephone	

Contractual details

CCG 1	
No. weeks Trust to prescribe	
Treatment reviews to be conducted by trust (frequency)	

CCG 2	
No. weeks Trust to prescribe	
Treatment reviews to be conducted by trust (frequency)	

CCG 3	
No. weeks Trust to prescribe	
Treatment reviews to be conducted by trust (frequency)	