Guidelines for the Initiation and On-going Treatment of Rifaximin for Preventing Episodes of Overt Hepatic Encephalopathy

Indications for Rifaximin

Rifaximin is indicated for the reduction in recurrence of episodes of overt Hepatic Encephalopathy (HE) in patients ≥ 18 years of age.[1] NICE has recommended rifaximin as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or over.[2]

Rifaximin is recommended as an option in the treatment of clinically overt HE refractory to first line therapies as defined by West Haven Criteria Grade 1 – 4 or the Organisation Mondiale de Gastroenterologie Working Party (see Ferenci P, *et al.* Hepatology 2002; 35:716-21) as assessed by a Consultant Hepatologist or a Consultant Gastroenterologist with experience in treating liver disease, once other causes of encephalopathy (electrolyte abnormalities, sepsis, anaemia, constipation, dehydration, drugs such as diuretics and analgesics) have been excluded.

The patient should be using regular aperients correctly and have documented episodes of validated breakthrough/refractory HE. In subclinical HE corroborative evidence of encephalopathy should be supplied, for example EEG studies supportive of HE and/or evidence of cirrhosis/porto-systemic shunting.

The role of psychomotor testing and evaluation in the initiation of rifaximin for minimal-HE needs further investigation. Initiation of rifaximin cannot be recommended purely on the grounds of psychomotor impairment or behavioral change at present; consider enrolment in clinical trials.

At present there is no suitable alternative to rifaximin that has an equivalent evidence base or safety profile.

It should be noted that rifaximin is to be used in combination with aperients such as lactulose (or polyethylene glycol 3350-electrolyte solution), which have been shown to reduce the symptoms of encephalopathy.

The role of rifaximin for patients in whom the DVLA has previously withdrawn their driving license due to episodes of clinically overt HE has not been established. Clinicians are advised to refer patients whose symptoms resolve with regular rifaximin use back to the DVLA for advice.

General Prescribers (GPs) should not be asked to initiate treatment with rifaximin but may be asked to prescribe on-going supplies in those patients in whom rifaximin treatment has proven successful.

Responsibilities of clinician initiating treatment – secondary care

1. Ensure the patient meets the criteria for treatment with rifaximin by checking full details of patient's medical records and medication history (i.e. G.P. records)
2. Discuss benefits and side effects of treatment with the patient and provide patient information leaflet (PIL) on rifaximin
3. Prescribe one month's supply of treatment. (The published data used rifaximin as a regular daily prescription, but intermittent supervised trials of therapy withdrawal to assess the need for continuation are to be encouraged as long as the patient will not come to harm)
4. Clinical assessment at one month, to include renal and liver function tests and full blood count.
5. If the patient is deriving benefits from rifaximin supply a further month's supply
6. Contact the patient's GP requesting on-going prescribing of rifaximin
7. Review the patient every 3 to 6 months to undertake routine clinical blood monitoring, review efficacy of and confirm the need for continuing treatment with rifaximin with the GP
8. Treatment beyond six months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction

Responsibilities of clinician prescribing on-going rifaximin treatment – primary care

1. Agree to supply on-going prescribing of rifaximin
2. Monitor the patient's clinical condition, such as temperature, blood in stools and change in symptoms
3. Prescribe rifaximin in response to consultant's feedback after each 3 to 6 month follow-up appointment

Responsibilities of the Patient

1. Report to the doctor if there is not a clear understanding of the treatment and share any concerns in relation to treatment
2. Adhere to the treatment prescribed
3. Report any adverse effects whilst on treatment with rifaximin
4. Inform specialist or GP of any medication being taken, including over-the-counter products

Prescribing information[1]

This information should be read in conjunction with the current BNF and manufacturer's SPC.

Licensed indications
Rifaximin is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

Dosage & Administration
Recommended dose: 550 mg twice a day.
The clinical benefit was established from a controlled study in which subjects were treated for 6 months. Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction.

Contraindications
- Documented drug allergy, rash and/or hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients
- Pregnancy
- Prior non-response to therapy
- Intestinal obstruction

Cautions
- *Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out
- Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of rifaximin with other rifamycins is not recommended
- Patients should be informed that despite the negligible absorption of the drug (less than 1%), like all rifamycin derivatives, rifaximin may cause a reddish discolouration of the urine
- The lack of safety data in Child-Pugh C cirrhosis (or MELD>25) means that the drug should be used with caution in advanced liver disease
- Due to the effects on the gut flora, the effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. However, such interactions have not been commonly reported. It is recommended to take additional contraceptive precautions, in particular if the oestrogen content of oral contraceptives is less than 50 micrograms
- Fertility and lactation: It is unknown whether rifaximin or its metabolites are excreted in human milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy taking into account the benefit of breast feeding for the child and the benefit for the woman

Adverse effects
The most common reported side effects in trials were psychiatric disorders, dizziness, headache, dyspnoea, abdominal pain and distension, nausea and vomiting, ascites, rashes, muscle spasm, arthralgia and peripheral oedema. Refer to the Summary of Product Characteristics for full details.

Drug interactions
Refer to the Summary of Product Characteristics for details.

References:
1. Rifaximin Summary of Product Characteristics, available at: http://www.medicines.org.uk/emc/medicine/27427
2. NICE Technology Appraisal guidance - TA337 (March 2015; reviewed June 2018): Rifaximin for preventing episodes of overt hepatic encephalopathy.