AMBER 2 GUIDANCE FOR THE PRESCRIBING OF RIFAXIMIN FOR HEPATIC ENCEPHALOPATHY

1. Background

Rifaximin is a non-absorbed semi-synthetic derivative of rifamycin with a wide spectrum of antibacterial activity against aerobic and anaerobic gram-positive and gram-negative organisms. It acts by binding to the ß-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. In hepatic encephalopathy (HE) it is thought to reduce the colony count of ammonia-producing gut flora and to decrease the systemic absorption of ammonia from the intestinal lumen.

Note

Rifaximin is also licensed for traveller's diarrhoea (at a different dose to that mentioned below) - not routinely commissioned within the Humber Sub-Integrated Care System Locality. Rifaximin is also approved for treatment of bacterial colonisation of small bowel in immunodeficient patients- (at a different dose to that mentioned below). This is an unlicensed indication for prescribing by Consultant Immunologist only (Red indication).

2. Indication

Reducing recurrence of episodes of overt hepatic encephalopathy in adults (NICE TA337).

3. Initiation/Dose/Duration

Rifaximin should only be initiated by a Consultant Hepatologist or Consultant Gastroenterologist, with a recognised interest in liver disease.

Initial 8-week treatment to be prescribed by the specialist. It is anticipated that the GP will prescribe following the one-month specialist review. Specialist team will advise on ongoing treatment, following review and treatment is not to be stopped unless advised by specialist. The specialist will continue to review the patient at 3 – 6 monthly intervals.

Initially, rifaximin tablets 550mg will be prescribed orally, twice daily.

- Transfer of monitoring and prescribing to Primary care is normally after the patient is on regular dose and with satisfactory investigation results for at least 4 weeks.
- The duration of treatment 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.
  Do not stop rifaximin treatment, without confirmation / discussion with the specialist.

The clinical benefit was established in a controlled study in which subjects were treated for 6 months. Treatment beyond this period should take into consideration, the individual balance between benefits and risks, including progression of hepatic dysfunction.

Rifaximin may be administered with or without food and should be given with a glass of water.

4. Contraindications and Cautions

Contraindications

- Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients.
- Cases of intestinal obstruction.

Cautions

- Hepatic Impairment: use with caution in patients with severe (Child-Pugh C) hepatic impairment and in patients with MELD (Model for End-Stage Liver Disease) score > 25.
- The potential association of rifaximin treatment with Clostridioides difficile associated diarrhoea and pseudomembranous colitis (PMC) cannot be ruled out. Patients who develop signs of pseudomembranous colitis after starting Rifaximin (diarrhoea, fever and abdominal pain) will be advised to contact their physician immediately.
- Rifaximin may cause: rashes and itching, or more general side effects such as: nausea, abdominal pain, dizziness, fatigue, headaches, muscle cramps and joint pain. See Section 5 below, regarding recommended action, should these more general side effects occur.
- Pregnancy and breastfeeding – see Section 8 below.

5. Adverse effects

Adverse effects	Action for GP
Nausea, vomiting, abdominal pain, flatulence, diarrhoea.	Discuss with Specialist.
Dyspnoea.	
Headache, dizziness.	
Muscle spasm.	
Rash, pruritus.	

6. Drug interactions

Due to the negligible gastrointestinal absorption of orally administered Rifaximin (less than 1%), the systemic drug interaction potential is low.

The following drugs are known or suspected interactions:	
Interacting Drug	Advice
Other rifamycins (e.g. rifampicin).	Avoid concomitant use.
Combined Oral Contraceptives.	Reduced effects of COCs have not been reported. However, due to effects of rifaximin on gut flora, manufacturer recommends taking additional contraceptive precautions, in particular, if the OC oestrogen content is below 50 micrograms.
In healthy subjects, clinical drug interaction studies demonstrated that rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates. However, in hepatic impaired patients it cannot be excluded that rifaximin may decrease the exposure of concomitant CYP3A4 substrates administered (e.g. warfarin, antiepileptics, antiarrhythmics), due to the higher systemic exposure with respect to healthy subjects.	

Details of contraindications, cautions, drug interactions and adverse effect listed above are not exhaustive. For further information always check with BNF http://www.bnf.org.uk or SPC (www.medicines.org.uk)

7. Monitoring

Baseline

Clinical assessment at 1 month, by the initiating Consultant:

Blood monitoring: LFTs; FBC; U&Es, at 1 month.

Ongoing

Because of negligible absorption of the drug, there are no *specific* monitoring requirements for rifaximin. However, it is worth monitoring parameters of the patient's clinical condition, such as: temperature; blood in stools, or change in symptoms.

Routine clinical blood monitoring, every three to six months, thereafter, to assess any renal and ongoing progression of hepatic dysfunction.

- Consultant Hepatologist or Consultant Gastroenterologist will inform patient about expected response to treatment and side effects of medication.
- If there is no improvement in the level of encephalopathy or failure to prevent hospital admissions with hepatic encephalopathy, rifaximin will be stopped.
- The onset of encephalopathy is an indication for liver transplant so patients who are considered suitable candidates will be assessed. At transplantation, rifaximin will be stopped.

- In those patients who are not suitable for transplant but have responded to rifaximin, the drug will be continued and its use reviewed at clinic visits.

8. Pregnancy and Breast Feeding

Pregnancy

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 GP and the specialist. The GP should discuss with specialist if patient is pregnant or planning pregnancy.

Breast Feeding

Present in milk in small amounts. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from rifaximin therapy considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

9. Information for patient

Patients should be informed of risks and benefits of treatment and expected follow up by specialist team.

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.

10. References

- BNF monograph for rifaximin: https://bnf.nice.org.uk/drugs/rifaximin/
- Rifaximin 550mg tablet Summary of Product Characteristics: https://www.medicines.org.uk/emc/product/2976/smpc

<table>
<tr><td rowspan="5">Document and version control</td><td colspan="4">This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.</td></tr>
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