Dorset Medicines Advisory Group

SHARED CARE GUIDELINE FOR PRESCRIBING RIFAXIMIN (TARGAXAN®) ▼FOR PREVENTING EPISODES OF OVERT HEPATIC ENCEPHALOPATHY IN ADULT PATIENTS (IN ACCORDANCE WITH NICE TA 337)

INDICATION FOR USE

The summary of product characteristics (SPC) for Rifaximin states it is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age. In the pivotal study, described in the SPC, 91% of the patients were using concomitant lactulose.

Please note that this shared care guidance document only refers to rifaximin as Targaxan® (550mg tablets), and that the other existing preparation, Xifaxanta® 200mg tablets (licensed for travellers' diarrhoea) is outside the scope of this document.

NICE GUIDANCE

NICE TA 337: Rifaximin for preventing episodes of overt hepatic encephalopathy states: "Rifaximin is recommended, within its marketing authorisation, as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older."

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of rifaximin can be shared between the specialist setting and the patient's GP. GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Specialist Responsibilities	
1	Assessment of the patient as a candidate for treatment with rifaximin in line with NICE TA337 and local pathways for management of overt hepatic encephalopathy.
2	Consideration of any contra-indications, special warnings and potential drug interactions of the intended treatment regimen. See section below for more details.
3	Counselling of the patient with regard to potential side effects of treatment.
4	A minimum of one month's treatment should be dispensed by the hospital. The GP must be informed **in writing** of the patient's diagnosis, the treatment regimen to be used (in particular whether rifaximin is to be prescribed concomitantly with lactulose), start date of treatment, review information and management advice. Where appropriate, the GP can be asked to take over the future prescribing of repeat treatment within this guidance.

Specialist Responsibilities	
5	Review of the patient's treatment in regular outpatient appointments. Where treatment continues beyond six months the specialist should ensure a regular risk-benefit analysis is undertaken as part of ongoing review. Changes to therapy as a result of these reviews (or at any other time) should be reported to the GP promptly.
6	Notifying the patient's GP if treatment is to be discontinued and the reason for this.
7	Ensuring that clear arrangements are in place for GP to obtain back up, advice and support.
8	This medicinal product is subject to additional monitoring under the MHRA black triangle scheme ▼. The specialist should report known or suspected adverse events to the MHRA via the Yellow Card scheme and share this information with the GP.

General Practitioner Responsibilities (where initiation is within a specialist setting and prescribing has been transferred to primary care)	
1	Referral of the patient to the specialist.
2	Responding to the request from the specialist to take on prescribing as soon as is practicable.
3	Continue to prescribe the therapy requested, under the guidance of specialist.
4	Monitor patient at regular intervals in conjunction with specialist.
5	Refer queries to the specialist, e.g. regarding treatment/side effects, and concerns about compliance with treatment.
6	This medicinal product is subject to additional monitoring under the MHRA black triangle scheme ▼. The GP should report known or suspected adverse events to the MHRA via the Yellow Card scheme and share this information with the specialist.
7	Stopping treatment on instruction of the specialist.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate consultant and GP appointments.
3	Share any concerns in relation to treatment.
4	Use written and other information on the medication.
5	Seek help urgently from the GP or specialist service if suffering with suspected side effects, or otherwise feeling unwell during treatment.
6	If the patient is seen by another service, clinic or hospital, they should advise the healthcare professionals offering treatment about their treatment, particularly if new medicines are administered or prescribed.

SUPPORTING INFORMATION

Dosage and Administration

Recommended dose: 550 mg twice a day. Rifaximin should be taken orally with a glass of water, with or without food.

Duration of treatment

The clinical benefit was established from a controlled study in which subjects were treated for 6 months. The SPC states that "Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction." It also notes: "Treatment with rifaximin for periods up to 24 months (OLE study RFHE3002) did not result in any loss of effect regarding the protection from breakthrough overt HE episodes and the reduction of the burden of hospitalization. Time to first breakthrough overt HE episode analysis showed long-term maintenance of remission in both groups of patients, new and continuing rifaximin."

Contraindications to rifaximin treatment:

- Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients listed in the summary of product characteristics.
- Cases of intestinal obstruction.
- Patient aged <18 years.
- Patient is pregnant or breastfeeding.

Special considerations

- 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.
- 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.
- 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. These patients were excluded from the pivotal trial. However the SPC also states: "Clinical data available for patients with hepatic impairment showed a systemic exposure higher than that observed in healthy subjects. The systemic exposure of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. The increase in systemic exposure to rifaximin in subjects with hepatic impairment should be interpreted in light of rifaximin gastrointestinal local action and its low systemic bioavailability, as well as the available rifaximin safety data in subjects with cirrhosis. Therefore no dosage adjustment is recommended because rifaximin is acting locally."

Potential side effects

Side effects listed in the BNF (in order of frequency): nausea, vomiting, abdominal pain, flatulence, diarrhoea, dyspnoea, headache, depression, dizziness, muscle spasm, rash, pruritus; *less commonly:* anorexia, taste disturbances, dry mouth, peripheral oedema, sleep disturbances, anxiety, memory impairment, convulsions, hypoaesthesia, paraesthesia, antibiotic-associated colitis, influenza-like symptoms, dysuria, polyuria, glycosuria, polymenorrhoea, blood disorders, hyperkalaemia; rarely blood pressure changes, constipation; *also reported:* syncope

Interactions

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.

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 µg

The lists of potential side effects and potential drug interactions included within this document are not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs (correct at March 2015, from BNF):

Targaxan® tablets, f/c, rifaximin 550mg, 56-tab pack = £259.23

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References

- Summary of Product Characteristics for Targaxan® 18mg tablets (Norgine Limited, accessed 16/04/2015)
- NICE Technology Appraisal: Rifaximin for preventing episodes of overt hepatic encephalopathy (accessed 16/04/2015)