GUIDANCE 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. Treatment for overt hepatic encephalopathy should be escalated according to the patients response starting with lactulose 30ml TDS and only adding in rifaxamin when lactulose has not resolved symptoms. If lactulose works then rifaxamin should not be added. If the patient has had more than on episode of overt hepatic encephalopathy and is not taking lactulose then lactulose should be used again before adding rifaximin.

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."

Please note that this 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.

Duration of Treatment

Duration > 6 months – In cerain circumstances Rifaximin may be continued for >6 months. The bacterial production of ammonia does not change after 6 months and encephalopathy will present again if rifaximin is stopped and the liver is still unable to metabolise the ammonia. The only patients where treatment would be stopped is in those where there has been an improvement in the capacity of the liver to metabolise the ammonia. Rifaximin may be stopped in decompensated alcoholic liver disease as there is a possibility that the patients liver function may improve when abstinent from alcohol. Rifaximin is unlikely to be stopped in other patients as stopping treatment post 6 months could result in an increase in hospital admissions.

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 (min 6 monthly.) **Where treatment is to continue beyond six months the specialist should ensure a regular risk-benefit analysis is undertaken**. If treatment is to continue beyond 6 months or there are changes to therapy as a result of these reviews the GP should be notified 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.

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."