Rifaximin *(Targaxan®)*

FOR PRESCRIBING RIFAXIMIN (TARGAXAN®) FOR REDUCTION IN RECURRENCE OF EPISODES OF OVERT HEPATIC ENCEPHALOPATHY IN ADULT (≥ 18 YEARS OF AGE) PATIENTS

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines how responsibility for prescribing rifaximin for reduction in recurrence of episodes of overt hepatic encephalopthy in patients ≥ 18 years of age might be shared between the specialist and general practitioner (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 between the specialist, GP and patient. 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. Patients with hepatic encephalopathy are under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes this medication legally assumes clinical responsibility for rifaximin and the consequences of its use.

RESPONSIBILITIES and ROLES

	Specialist (Consultant Gastroenterologist) responsibilities
1	Assess the patient as a candidate for treatment with rifaximin in line with NICE guidance and local pathways for management of overt hepatic encephalopathy.
2	Consider any potential drug interactions of the intended treatment regimen with drugs that the patient may already be taking. See drug interactions section below for more details.
3	Initiate treatment and provide at least 28 days supply and until GP agrees to shared care.
4	Discuss the benefits and side effects of treatment with the patient and ensure the patient understands the nature and complications of drug therapy and their role in adhering to therapy.
5	Ask the GP whether he or she is willing to participate in shared care, and agree with the GP as to who will discuss the shared care arrangement with the patient.
6	Inform the GP in writing of the patient's diagnosis, the treatment regimen to be used, start date of treatment, intended duration of treatment and management advice. Where appropriate the GP can be asked to take over the future prescribing of repeat treatment within this guidance.
7	Review the patient's condition and monitor response to treatment regularly as part of routine clinic follow- up. Changes to therapy as a result of these reviews (or at any other time) and missed clinic appointments should be reported to the GP promptly.
8	Give advice to the GP on when to stop treatment.
9	Report adverse events to the MHRA (yellow card scheme) and share this information with the GP.
10	Ensure that clear backup arrangements exist for GPs to obtain advice and support.

	General Practitioner responsibilities
1	Referral of the patient to the specialist.
2	Reply to the request from the specialist to take on prescribing of this medication as soon as practicable.
3	Continue to prescribe the therapy requested, under the guidance of the specialist.
4	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.
5	Consider any potential drug interactions of the intended treatment regimen with drugs that the patient may already be taking, or any newly-initiated drugs. See drug interactions section below for more details.
6	Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment.
7	Stop treatment on the advice of the specialist.
8	Report adverse events to the specialist and MHRA (yellow card scheme).

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 Share any concerns in relation to treatment with the medicine.
3 Report any adverse effects to the specialist or GP whilst taking the medicine.
4 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.

BACK-UP ADVICE AND SUPPORT

Contact details	*Telephone No.*	*Bleep*	*Fax*	*Email address:*
Dr Moby Joseph, Consultant Hepatologist.	01793604143	-	-	moby.joseph@gwh.nhs.uk
Dr Andrew Claridge, Clinical Lead Gastroenterology	01793605270	-	-	Andrew.Claridge@gwh.nhs.uk
Gastroenterology Registrar	01793604020 (switchboard) then ask to bleep them.			
Medicines Information	01793605369	-	-	medinfo@gwh.nhs.uk

SUPPORTING INFORMATION

➢ Background Information

Hepatic encephalopathy is a neurological complication of liver disease with devastating effects on the affected patients, their family and carers. While HE is commonly seen in decompensated cirrhosis- 40% of such patients will be affected- it is usually episodic and precipitated by identifiable and treatable causes, such as infection. A minority of patients with recurrent disease and no reversible cause may benefit from treatment with Rifaximin, which has recently been the subject of the **NICE technology appraisal guidance [TA337], March 2015[1,2,3].**

Rifaximin is to be prescribed within the terms of its licence, its marketing authorisation and NICE guidance, i.e. as an option to reduce recurrence of episodes of overt hepatic encephalopathy.

Rifaximin is considered as an addition to lactulose and after potential precipitating factors for HE have been investigated, identified and addressed.

How is Hepatic Encephalopathy Defined?

- Hepatic encephalopathy (HE) is a *brain dysfunction* caused by *liver insufficiency* and/or porto-systemic shunting; it manifests as a *wide spectrum of neurological or psychiatric abnormalities* ranging from subclinical alterations to coma
- *Recurrent HE* denotes more than 1 episode within a 6-month timeframe
- *Overt HE* denotes clinically demonstrable brain dysfunction, corresponding to West Haven criteria 2-4, such as:
    - Lethargy, disorientation, dyspraxia, asterixis
    - Somnolence, gross disorientation, bizarre behaviour
    - Coma

What is Rifaximin?

Rifaximin is a minimally-absorbed derivative of the antibiotic rifamycin, which decreases the intestinal production and absorption of ammonia, a key player in the pathogenesis of HE.

What is the aim of therapy?

To reduce "the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older". Additional aims include:

- Reduction in hospital admissions
- Reduction in hospital length of stay
- Improvement in quality of life

How is treatment effect evaluated?

- Regular review in Gastro/Hepatology Outpatients (e.g. 4-12 week intervals, as appropriate)
- Maintenance/preventative therapy: reduction in number and frequency of episodes of overt HE; reduction in associated hospital admissions
- "Breakthrough" episodes of overt HE (usually requiring hospital admission) will be examined by a Consultant Hepatologist on a case-by-case basis to determine whether continuation of treatment is appropriate
- Prospective audit of use in secondary care

Time to Response

As this is a therapy to reduce recurrence, there is no specific time to response.

Pre-Treatment Assessment

Pre-treatment assessment is conducted by a specialist (Consultant Hepatologist).

Ongoing Monitoring

Ongoing monitoring is conducted by a specialist (Consultant Hepatologist).

➢ Dosage and Administration

Rifaximin 550mg, orally, twice daily. The dose should be taken with a glass of water and can be administered with or without food.

No dosage adjustments are necessary in the elderly or those with hepatic impairment although caution is advised in those patients with severe hepatic impairment (Child-Pugh C or MELD score >25). Caution is also advised in patients with impaired renal function.

➢ Duration of Treatment

Decision to be made in collaboration with/by a Consultant Gastroenterologist

- Typically for 6 months before re-evaluation. If treatment is to continue beyond 6 months the Specialist must give explicit advice on how to review ongoing treatment.
- May be stopped in the event of significant improvement or deterioration in liver function (e.g. with antiviral therapy, or in context of liver failure, respectively)
- Until liver transplantation or death
- Evidence of lack of efficacy (e.g. further recurrent episodes with other precipitants, such as infections or GI bleeding or electrolyte disturbance).

➢ Contraindications and Precautions

Hypersensitivity to rifaximin, rifamycin-derivatives or any of the tablet excipients, and in cases of intestinal obstruction.
Patients aged < 18 years.

Pregnancy and breastfeeding:

Pregnancy: manufacturer advises avoid—toxicity in animal studies
Breastfeeding: rifaximin or its metabolites are unlikely to be present in milk in significant amounts, but manufacturer advises avoid.

➢ 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.

➢ Potential Adverse Effects

The side effect profile is very good as the drug is minimally absorbed. Side effects are usually mild or moderate and include: 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.

➢ Drug Interactions

Concomitant administration of rifaximin with other rifamycins is not recommended.
The effectiveness of oral contraceptives may be reduced with concomitant use of rifaximin due to effects on the gut flora. Additional contraceptive precautions are recommended particularly if the oestrogen content of oral contraceptives is less than 50 micrograms.
Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein such as ciclosporin.
In hepatic impaired patients it cannot be excluded that rifaximin may decrease the exposure of concomitant CYP3A4 substrates administered (e.g. warfarin, antiepileptics, antiarrhythmics[).4]

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 July 2016, from BNF):

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

References

1. NICE technology appraisal guidance [TA337]. Rifaximin for preventing episodes of overt hepatic encephalopathy. March 2015.
2. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. Journal of Hepatology/Hepatology December 2014.
3. Bass N et al. Rifaximin Treatment in Hepatic Encephalopathy. N Engl J Med 2010; 362:1071-81
4. Summary of Product Characteristics for Targaxan (Norgine Limited, accessed online 19/7/2016).

Document details

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