HERTFORDSHIRE AND WEST ESSEX AREA PRESCRIBING COMMITTEE (APC)
NICE TECHNOLOGY APPRAISALS – RECOMMENDED

NICE TA337 Rifaximin for preventing episodes of overt hepatic encephalopathy, March 2015

RECOMMENDED FOR RESTRICTED USE

Name: generic (trade)	What it is	Indication	Date decision last revised	Decision status	NICE / SMC Guidance
Rifaximin (Targaxan®)	semi-synthetic derivative of the antibiotic rifamycin	reducing the recurrence of episodes of overt hepatic encephalopathy	HMMC April 2015 WEMOPB August 2015	Final	NICE TA 337 recommended SMC – accepted for use

Recommendation: RECOMMENDED FOR RESTRICTED USE:

- Rifaximin (550mg twice a day) is recommended as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older as add on therapy to lactulose (unless contra-indicated/not tolerated) when there is recurrent hepatic encephalopathy on lactulose alone.
- Treatment is for secondary care specialist initiation only.
- Once patient is stabilised on rifaximin, prescribing responsibility may be transferred to primary care.
- Monthly prescriptions only should be prescribed.
- Patients should continue to receive regular follow-up by secondary care specialists.
- Specialist advice to GPs to include when and how to stop rifaximin and the ongoing treatment plan following 6 months of treatment (to confirm that the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction have been considered and rifaximin treatment is to continue or stop).
- GPs should regularly review patients and seek advice from the specialist: on any aspect of patient care that is of concern; if there is continued alcohol intake; if there are significant adverse reactions; if there is poor adherence; if the patient's condition deteriorates: following 6 months of treatment.

- The use of Rifaximin 200mg for any indication has not been considered and is **NOT** recommended.

Background information for Rifaximin (from SPC – refer to SPC for full details)

Dosage and Administration

- Recommended dose: one 550 mg tablet, twice a day taken orally with a glass of water (with or without food).
- 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.

Monitoring

The SPC does not identify any specific monitoring requirements.

Contraindications and precautions for use

Contraindications:

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

Special warnings/precautions:

- 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.
- 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.
- Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein such as ciclosporin is needed.
- Both decreases and increases in international normalized ratio (in some cases with bleeding events) have been reported in patients maintained on warfarin and prescribed rifaximin. If co-administration is necessary, the international normalized ratio should be carefully monitored with the addition or withdrawal of treatment with rifaximin. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.
- This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'

Side Effects

Common adverse events (occurring in ≥1/100 to <1/10 of patients): depression, dizziness, headache, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia, and peripheral oedema.

Drug Interactions

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, oral contraceptives), due to the higher systemic exposure with respect to healthy subjects.

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Cost (adapted from the NICE Costing Report)
- Rifaximin costs £259.23 for 56 x 550mg tablets (annual cost £3,370).
- Lactulose annual costs approx. £124 without rifaximin; £111 with rifaximin.

Further Information on rifaximin
- Rifaximin is a semi-synthetic derivative of the antibiotic rifamycin. It decreases intestinal production and absorption of ammonia, which is thought to be responsible for the neurocognitive symptoms of hepatic encephalopathy, thereby delaying the recurrence of acute episodes.
- Rifaximin has a broad spectrum of activity with very low absorption from gastro-intestinal tract.
- Expert clinical opinion given to NICE suggests that people may continue to use rifaximin until death or until they have a liver transplant.

Further Information on Hepatic Encephalopathy
- Hepatic encephalopathy is defined based on the severity of clinical symptoms of mental deterioration using the Conn grade. It may be classified as covert or minimal (Conn grade 0 or 1) or overt (Conn grade 2, 3 or 4). When people are in remission or have minimal hepatic encephalopathy, condition may be managed at home under secondary care. However, if a person has an acute overt episode they are often admitted to hospital for treatment.
- The current standard of care is treatment with lactulose.

Refer to Summary of Product Characteristics for further prescribing information on rifaximin
http://www.medicines.org.uk/emc/

Reference:

- NICE TAG 337 – Rifaximin for preventing episodes of overt hepatic encephalopathy, March 2015 http://www.nice.org.uk/guidance/ta337
- Midland Therapeutic Review and Advisory Committee; Template effective shared care agreement; Rifaximin; Feb 2014 https://www.centreformedicinesoptimisation.co.uk/

Version	2.0 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of ENHCCG and HVCCG headers
Developed by	Hertfordshire Pharmacy and Medicines Optimisation Teams East and North Herts CCG and NHS Herts Valleys CCG
Approved by	HMMC, WEMOPB
Date approved/updated	HMMC April 2015, WEMOPB August 2015
Review date:	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0 Updated: • Special warnings/precautions in line with SPC accessed 15/04/24. • Drug interaction in line with SPC accessed 15/04/24.