Rifaximin for the treatment of chronic hepatic encephalopathy

Recommendation

In line with NICE TA 337 Rifaximin has been approved for preventing episodes of hepatic encephalopathy in people aged 18 years or older. It will only be initiated by a consultant gastroenterologist who will continue prescribing until the patient has been reviewed at 4-8 weeks. Repeat prescribing will be undertaken by the patient's GP but the patient will be reviewed every 6 months by the consultant gastroenterologist.

Approved by: East Kent Prescribing Group *(Representing Ashford CCG, Canterbury and Coastal CCG, South Kent Coast CCG and Thanet CCG)*
Date: Jan 2016
Reviewed: April 2019
Address: c/o *Canterbury and Coastal CCG, Ground Floor, Council Offices, Military Road, Canterbury, Kent,CT1 1YW*
Contact: T: 01227 791267 | E: accg.eastkentprescribing@nhs.net

Rifaximin for the treatment of chronic hepatic encephalopathy

East Kent Hospitals University NHS Foundation Trust

Guideline for the use of Rifaximin for the Treatment of Hepatic Encephalopathy

Version	**1.2**
Ratified by	**East Kent Prescribing Group (once updates made) and EKHUFT Drug and Therapeutics Committee**
Date Ratified	**16th Sept 2015 (Both)**
Name of originator/author	**Dr A Muller, Consultant Gastroenterologist** **Carol Walker, Prescribing Support Pharmacist**
Division Responsible for Implementation	**UCLTC**
Date Issued	**Jan 2016**
Date Reviewed	**April 2019**
Target Audience	**Trust Gastroenterologists, GPs, Trust Pharmacists**

Version control schedule

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Version	Date	Author	Status	Comment
0.1	June 2015	C Walker	1st draft	Initial draft for comments
0.2	Aug 2015	C Walker	2nd draft	Email queries answered from Dr Shawcross, Kings Trust format
1.0	Aug 15	C Walker Dr AF Muller	Final version	Discussion between CW and AFM for final guideline
1.1	Sept 15	CWalker	Update following EKPG	Under "Outpatients" sentence added stating Trust Gastroenterologists will continue to prescribe rifaximin until they have reviewed the patient following at least 28 days of treatment after which the GP will be asked to take over prescribing.
1.2	Jan 16	CWalker	Following comments by Heather Lucas	Change liver function tests to at least every six to fit in with clinic visits (from every three months).
1.3	Apr 19	CWalker	Gurpreet Virdi and Dr Andrew Frank Muller	No Changes

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Guideline for the use of rifaximin for the treatment of chronic hepatic encephalopathy

Summary

This guideline is to aid the prescribing of rifaximin for hepatic encephalopathy (HE)in primary and secondary care.

Introduction

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 beta subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. In hepatic encephalopathy it is thought to reduce colony count of ammonia producing gut flora and to decrease the systemic absorption of ammonia from the intestinal lumen. Increased amounts of ammonia are thought to be responsible for the neurocognitive symptoms of HE. Rifaximin is effective in reducing the recurrence of HE episodes and is well tolerated. Treatment may improve quality of life, prevent admissions to hospital, reduce mortality and carer burden.

Purpose and Scope

These guidelines are for adult patient both as inpatients and outpatients who have had an episode of hepatic encephalopathy. Rifaximin can only be initiated by a consultant Gastroenterologist.

Indication

- Rifaximin should only be initiated by a Trust Gastroenterologist
- Rifaximin is approved for treatment of chronic low grade hepatic encephalopathy (impairing quality of life) and/or the secondary prevention of recurrent overt hepatic encephalopathy in patients with cirrhosis who have failed standard therapy.
- Standard therapy is defined as:
    - Removal/correction of precipitating factors
    - Laxatives (any) titrated to produce two soft stools daily
- It should not be used for patients with:
    - Acute hepatic encephalopathy
    - Hepatic encepahalopathy secondary to GI bleeding
    - A recent history of Clostridium difficile infection (within last six month)

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- Who are actively drinking alcohol to excess which negates any positive effect . Drinking alcohol within the usual safe limits would not preclude its use specifically with non-alcohol aetiologies.
- Who are currently being treated acutely with other intravenous antibiotics eg Tazocin or long term antibiotics such as norfloxacin (please discuss with microbiology or Kings if in doubt) to avoid development of *Clostridium difficile* and bacterial resistance.

Place in therapy: Inpatients

- The use of rifaximin is not indicated in the acute setting in a patient with chronic liver disease admitted wit hepatic encephalopathy (HE) or developing HE during their hospital stay.
- The cause for the development of HE should be investigated (ie underlying GI bleed, infection, metabolic disturbance) and treated appropriately. There will though be a small number of patients with spontaneous HE with no obvious precipitant.
- Patients will receive the current standard treatment for HE consisting of

  1) Lactulose 15-20mls TDS to ensure that the patient is opening their bowels 2-3 times a day

  2) daily or twice daily enemas initially to ensure bowels being opened regularly.

- If the patient responds to this treatment consider initiating rifaximin at the follow up clinic.
- If this is a second admission for HE consider initiating rifaximin on discharge.
- **Intractable HE:** If, with the above treatment and despite a stool frequency of 2-3 times daily for one week, the encephalopathy persists, and where available an EEG should be considered to confirm encephalopathy, rifaximin may be initiated at 550mg BD. Rifaximin will only be initiated by a hospital consultant gastroenterologist.
- **Palliative use:** if a patient is admitted with HE and a liver transplant has been ruled out then initiating rifaximin may help keep the patient out of hospital.

Place in therapy: Out patients

In the outpatient setting rifaximin will be prescribed for:

1. Patients with chronic liver disease who have a history of recurrent spontaneous encephalopathy despite taking regular lactulose and opening their bowels two to three times a day, as rifaximin is effective in preventing hospital admissions and has a significant cost saving
2. Patients who describe minimal HE, consisting of an altered sleep pattern, difficulty concentrating, struggling to do simple tasks and a reduced attention span, there being no obvious precipitant for these changes, the minimal HE persisting despite standard lactulose therapy. Unfortunately in minimal HE there are no standardised guidelines for assessing

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minimal HE in patients with cirrhosis. The neuropsychometric tests typically used to diagnose minimal HE can be time-consuming and cumbersome to perform, the result being very variable on the same day for the same patient.

A thorough history will therefore need to be taken in clinic with the patient and, where possible corroborated by a family member or close friend, with an assessment after 4 to 6 weeks of rifaximin to see whether there has been an improvement in symptoms. If there has been no improvement in quality of life the rifaximin will be discontinued. If there has been an improvement in the patient's quality of life the rifaximin will be continued. The hospital Gastroenterologist will be responsible for prescribing rifaximin until the patient has been assessed following at least 28 days treatment with rifaximin after which the GP may be asked to continue prescribing.

HE is an indication for liver transplantation and if appropriate the patients will be referred for assessment for this.

Dose

- 550mg twice daily

Duration

- Therapy should initially be for one month. Most patients who will respond will respond within 4 weeks. The patient should then be reviewed by a consultant Gastroenterologist and if there is a demonstrable improvement in symptoms then therapy can be continued. Improvement would be considered as a reduction in one grade or more of encephalopathy as defined by the Westhaven criteria, a reduction in admissions for encephalopathy, an improvement in neuropsychological function tests if available and/or an improvement in overall quality of life.
- If a patient responds they should remain on the drug life-long or until they have a liver transplant. There is no evidence to suggest stopping the drug as gut dysbiosis will rapidly recur.

Monitoring

- Liver function tests-baseline, month one and at least every 6 months thereafter.
- HE symptoms- Westhaven Grade every six months in clinic
- Admissions for encephalopathy
- An improvement in neuropsychological function (Trails A and B Test if available)
- Improvement in quality of life

If there is no improvement in the level of encephalopathy or failure to prevent hospital admissions with HE then the rifaximin will be stopped*. The onset of encephalopathy is an indication for liver transplant so patients who are suitable for liver transplantation will be referred to Kings Liver Unit

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for assessment for this and at the time of transplantation rifaximin will be stopped. In those patients who are not suitable for transplant but have responded to rifaximin, the rifaximin will be continued, patients being followed up every 6 months in clinic, or as dictated by clinical need. Please note this latter group of patients have a significantly reduced mortality with those patients with advanced liver disease having an expected 2 year survival of 35% (Childs Pugh C).

*HE may recur after rifaximin but a recent 7 centre UK audit (personal communication) has shown that even when it does, the number of admissions are reduced and the length of stay is invariably shorter. Furthermore, it probably reduces the severity of any HE episode. Also the Child Pugh and MELD score improve after 90 days in those taking rifazimin suggesting that I may have more far reaching impact by tempering endotoxemia, systemic inflammation and immune dysfunction that drive the various complications (personal communication, Dr Shawcross, Kings)

West Haven criteria

The severity of HE is graded with the West Haven Criteria; this is based on the level of impairment of autonomy, changes in consciousness, intellectual function, behaviour, and the dependence on therapy.

- Grade 1- Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade 2- Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour
- Grade 3- somnolence to semistupor but responsive to verbal stimuli; confusion; gross disorientation
- Grade 4 – Coma (unresponsive to verbal or noxious stimuli)

Prescribing

- Rifaximin can only be initiated by a trust consultant Gastroenterologist. The trust will supply the first month's treatment and aim to follow up in clinic in 4 to 6 weeks. The GP will need to prescribe from week 4. The trust will review HE patients and treatment at least every six months.
- Median duration of treatment is six to twelve months but may be longer depending on response.

Unwanted effects and contraindications

- Rifaximin may cause side effects of nausea, abdominal pain, dizziness, fatigue, headaches, muscle cramps and joint pain. It can also cause more serious side effects such as allergic reactions, rashes and itching.

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- Rifaximin can alter the normal bacteria in the colon and encourage overgrowth of some bacteria such as *clostridium difficile* which causes inflammation of the colon (pseudomembranous colitis). Patients who develop signs of pseudomembranous colitis after starting rifaximin (diarrhoea, fever and abdominal pain) will be advised to contact their physician immediately.
- Contraindicated in patients with rifamycin hypersensitivity.

Interactions

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

Advice to patients

If patients develop diarrhoea, fever and abdominal pain they will be advised to contact the gastroenterology consultant secretary (number will be on clinic letter) urgently to speak with a doctor from the gastroenterology team or on call gastroenterologist. Out of hours the patient should contact the out of hours GP service or attend A&E. Usually the rifaximin will be discontinued. There will be a letter given to patients with these contact details when they are prescribed rifaximin.

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6 Key Stakeholders, Consultation, Approval and Ratification Process

. Through Gastroenterology and UCLTC governance, East Kent Prescribing group, Drug and Therapeutics Committee

7 Review and Revision Arrangements

This document will be reviewed every 2 years

8 Dissemination and Implementation

This document will be stored on sharepoint available to all staff members,

9 Monitoring Compliance

This will be through Datix incident reporting

10 References

1. Summary of product characteristics Targaxan (Norgine) 11/1/2013 via https://www.medicines.org.uk/emc/medicine/27427
2. NICE TA 337 Rifaximin for preventing episodes of overt hepatic encephalopathy (TA337)
3. Kings College Hospital Guideline
4. St Georges Healthcare Guideline
5. MTRAC Commissioning Support Rifaximin 550mg tablets (Tragaxan) for the prevention of recurrence of episodes of overt hepatic encephalopathy. Jan 2014