Consider hepatic encephalopathy (HE) in patients with confirmed diagnosis of cirrhosis, ascites, and/or varices

**Administration**
- Add correct Read code to patient's notes (e.g. a code of J622-1 in EMIS)
- Arrange for electronic alert to be added to surgery system for all patients at risk of HE
- Leave appropriate notifications for Out of Hours providers that the patient is at risk of, or being treated for HE

**Pharmacological management of HE**
- Continue medicines prescribed in secondary care in line with local protocols
- Treatments for overt HE include:
  - lactulose:
    - dose should be titrated to achieve 2–3 soft stools per day
    - do not substitute with laxatives if this is not achievable
  - neomycin
- Options for the prevention of recurrent episodes of overt HE include:
  - lactulose
  - rifaximin-α:
    - may be prescribed in combination with lactulose
    - maintain HE-specific dosing of 550 mg twice a day

**Precipitating factors**
- Constipation
- Electrolyte disorder
- Gastrointestinal bleeding
- Over diuresis
- Infection
- Sedative medications

**Safety risks**
- Consider occupational hazards
- Patients who have hepatic cirrhosis with neuropsychiatric impairment should not drive and must notify the DVLA
  - Using dangerous equipment should be avoided

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- Electrolyte disorder
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**Still symptomatic**
- Persistent Grade 1* symptoms
- Gradually worsening Grade 1* symptoms
  - Check for any obvious precipitants (including infections) and treat accordingly
  - Ensure patient is adherent with treatment
  - Contact a liver specialist for advice

**Symptoms under control**
- Maintain medication reviews (no longer than 6 months apart)
- At every opportunity, including all consultations and medication reviews:
  - be alert and monitor closely for signs of deterioration
  - reinforce education on precipitating factors
  - reinforce advice around safety risks
- Be aware of drug interactions and contraindications when prescribing new drugs for other conditions

**Acute episode**
- Grade 2–4* symptoms
- Very drowsy
- Very confused
- Diminishing consciousness
  - Treat any obvious infection immediately
  - Contact a liver specialist for urgent admission
  - Arrange ambulance if patient is deteriorating rapidly or losing consciousness

**Patient stabilised and discharged from hospital**

*Grading of symptoms is detailed overleaf
Hepatic encephalopathy (HE)

- HE is a frequent complication of chronic liver disease and one of its most debilitating manifestations, severely affecting the lives of patients and their carers and increasing demand on the healthcare system\(^2\).
- It is a reversible condition caused by accumulation of toxins normally removed by the liver, such as ammonia\(^3\).
- HE has a wide spectrum of neurological and psychiatric manifestations, ranging from subclinical alterations to coma (see Table 1)\(^2\).

Pharmacological management

- Once any precipitating causes have been addressed, treatment aims to minimise the production and absorption of toxins (such as ammonia) in order to reduce symptoms\(^4,5\).
- Medication is usually initiated in secondary care at the time of diagnosis, but primary care may need to prescribe repeat doses in line with local arrangements.
- Prescription of CNS-altering drugs and sedatives should be avoided in patients with HE.
- Check summary of product characteristics before prescribing to rule out contraindications, precautions, and potential drug interactions.
- Treatment of overt HE:
  - lactulose:
    - non-absorbable polysaccharide that changes the pH of stools to prevent growth of bacteria that produce toxins, such as ammonia\(^4\)
    - starting dose of 30–50 ml 3 times daily; dose should be titrated to achieve 2–3 soft stools per day\(^4\)
    - if lactulose does not result in 2–3 soft stools per day do not substitute with laxatives, as it is not the laxative effect that is useful in the treatment of HE
  - non-absorbable antibiotics (short-term):
    - neomycin is licensed for the treatment of acute HE but is now rarely used due to adverse effects associated with cumulative systemic absorption, including deafness and renal failure\(^5,6\).
- Prevention of recurrent episodes of overt HE:
  - lactulose:
    - if lactulose does not result in 2–3 soft stools per day contact a specialist for guidance on management, such as using rifaximin-\(\alpha\) therapy, which is an amber drug usually initiated in secondary or tertiary care.

Table 1: Possible symptoms of HE\(^2\)

<table>
<thead>
<tr>
<th>Symptom grade</th>
<th>Symptom description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>psychometric or neuropsychological alterations on tests without clinical evidence of mental change</td>
</tr>
<tr>
<td>Covert</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>trivial lack of awareness</td>
</tr>
<tr>
<td></td>
<td>euphoria or anxiety</td>
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<tr>
<td></td>
<td>shortened attention span</td>
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<tr>
<td></td>
<td>impairment of addition and subtraction</td>
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<tr>
<td></td>
<td>altered sleep rhythm</td>
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<tr>
<td>Grade 2</td>
<td>lethargy or apathy</td>
</tr>
<tr>
<td></td>
<td>disorientation</td>
</tr>
<tr>
<td></td>
<td>obvious personality change</td>
</tr>
<tr>
<td></td>
<td>inappropriate behaviour</td>
</tr>
<tr>
<td></td>
<td>dyspraxia</td>
</tr>
<tr>
<td></td>
<td>asterixis</td>
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<tr>
<td>Overt</td>
<td>somnolence to semi-stupor</td>
</tr>
<tr>
<td>Grade 3</td>
<td>impaired responsiveness to stimuli</td>
</tr>
<tr>
<td></td>
<td>confusion</td>
</tr>
<tr>
<td></td>
<td>gross disorientation</td>
</tr>
<tr>
<td></td>
<td>bizarre behaviour</td>
</tr>
<tr>
<td>Grade 4</td>
<td>coma</td>
</tr>
</tbody>
</table>
non-absorbable antibiotics:
- rifaximin-α:
  - is licensed for the reduction in recurrence of episodes of overt HE in patients ≥18 years of age7
  - minimises the bacterial load in the gut, which reduces the production of ammonia and other compounds implicated in the pathogenesis of HE7
  - may be prescribed in combination with lactulose
  - recommended dose of 550 mg twice a day with or without food7

Monitoring

- Monitor patients in line with local arrangements with specialist care
- Urea and electrolytes should be monitored closely, especially in patients taking diuretics:
  - diuretics can cause hyponatraemia, hypokalaemia, or renal dysfunction, which are all triggers for HE

Safety

- For full details of possible adverse reactions please refer to summaries of product characteristics at www.medicines.org.uk/emc
- lactulose—common adverse reactions include flatulence, abdominal pain, nausea, and vomiting. If the dose is too high, diarrhoea will occur4
- neomycin—common adverse reactions include nausea, vomiting, diarrhoea, increased salivation, stomatitis, nephrotoxicity, ototoxicity, rise in serum levels of hepatic enzymes and bilirubin, blood dyscrasias, haemolytic anaemia, confusion, paraesthesia, disorientation, nystagmus, hypersensitivity reactions including dermatitis, pruritus, drug fever and anaphylaxis5
- rifaximin-α—common adverse reactions reported with rifaximin-α are dizziness, headache, depression, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia and peripheral oedema7

References


This supplement has been commissioned by Norgine Pharmaceuticals Limited. Norgine Pharmaceuticals Limited was able to suggest relevant experts to Chair the group, with final decisions on the remaining group members resting with the Chair and Guidelines. Norgine Pharmaceuticals Limited has reviewed the supplement for technical and scientific accuracy, and to ensure its compliance with appropriate regulations. Final editorial control has remained with the contributors and Guidelines. The views and opinions of the contributors expressed in this document are not necessarily those of Norgine Pharmaceuticals Limited, or of Guidelines, its publishers, advisers, or advertisers.

group members—Michelle Clayton (Chair, lecturer in liver care), Dr Richard Aspinall (consultant hepatologist), Dr Honor Merriman (general practitioner), Dr John O’Malley (general practitioner with special interest in gastroenterology)

conflicts of interest—Michelle Clayton has received honoraria, and travel and accommodation expenses from Norgine Pharmaceuticals Ltd for presenting at conferences and participating in advisory boards.
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Honor Merriman has previously received honoraria for participating in the development of a Guidelines algorithm, sponsored by Roche Diagnostics Ltd.
John O’Malley has received honoraria, and travel and accommodation expenses from Actavis UK Ltd, Norgine Pharmaceuticals Ltd, and Reckitt Benckiser Healthcare Ltd for presenting at conferences and participating in advisory boards.

Date of preparation: November 2016
TARGAXAN® 550 mg film-coated tablets.

REFER TO FULL SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) BEFORE PRESCRIBING

Presentation:
Film-coated tablet containing rifaximin 550 mg.

Uses:
Targaxan is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥18 years of age.

Dosage and administration:
Adults 18 years of age and over: 550 mg twice daily, with a glass of water, with or without food for up to 6 months.

Treatment beyond 6 months should be based on risk benefit balance including those associated with the progression of the patients hepatic dysfunction.

No dosage changes are necessary in the elderly or those with hepatic insufficiency. Use with caution in patients with renal impairment.

Contraindications:
Contraindicated in hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients and in cases of intestinal obstruction.

Warnings and precautions for use:
The potential association of rifaximin treatment with Clostridium difficile associated diarrhoea and pseudomembranous colitis cannot be ruled out.

The administration of rifaximin with other rifamycins is not recommended.

Rifaximin may cause a reddish discolouration of the urine.

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.

In hepatic impaired patients, rifaximin may decrease the exposure of concomitantly administered CYP3A4 substrates (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives).

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.

Ciclosporin may increase the rifaximin $C_{\text{max}}$

Pregnancy and lactation:
Rifaximin is not recommended during pregnancy.

The benefits of rifaximin treatment should be assessed against the need to continue breastfeeding.

Side effects:
Common effects reported in clinical trials are dizziness, headache, depression, dyspnœoa, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia and peripheral oedema.

Other effects that have been reported include: Clostridial infections, urinary tract infections, candidiasis, pneumonia cellulitis, upper respiratory tract infection and rhinitis. Blood disorders (e.g. anaemia, thrombocytopenia). Anaphylactic reactions, angioedemas, hypersensitivity. Anorexia, hyperkalaemia and dehydration. Confusion, sleep disorders, balance disorders, convulsions, hypoesthesia, memory impairment and attention disorders. Hypotension, hypertension and fainting. Hot flushes. Breathing difficulty, pleural effusion, COPD. Gastrointestinal disorders and skin reactions. Liver function test abnormalities. Dysuria, pollakiuria and proteinuria. Oedema. Pyrexia. INR abnormalities.

Legal category: UK - POM, Ireland - Prescription only.

Cost: UK - Basic NHS price £259.23 for 56 tablets. Ireland - €262.41 for 56 tablets

Marketing Authorisation number:
UK - PL 20011/0020. Ireland - PA 102/29/1

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Date of preparation: October 2016

United Kingdom - Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Medical Information at Norgine Pharmaceuticals Ltd on 01895 826606.

Ireland - Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafe@hpra.ie. Adverse events should also be reported to Medical Information at Norgine Pharmaceuticals on +44 1895 826606.