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Hepatic Encephalopathy
what you need to know

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Prescribing information can be found on page 4.

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Hepatic Encephalopathy Overview

Globally, **chronic liver disease affects an estimated 844 million** people[1] and accounts for approximately 4% of all deaths worldwide.[2] Hepatic encephalopathy (HE) is associated with a significant increase in mortality; survival after the first episode of HE is 42% at 1 year, decreasing to 23% at 3 years[3]

Chronic liver disease may lead to cirrhosis, which in turn leads to the development of HE in around half of all liver cirrhosis patients[3]

- In Europe alone, HE is estimated to affect up to 200,000 people[4]

HE can be a result of impaired liver function or portosystemic shunting and leads to a spectrum of neuropsychiatric abnormalities[5]

- HE can occur in any underlying liver disease and at any age[3]
- It can be classified into two distinct forms:[6]
  - Covert HE (outwardly normal mental and neurologic function but with abnormalities on psychometric testing)
  - Overt HE (where neurological and neuropsychiatric abnormalities are clinically apparent)

HE is a reversible condition[7] caused by the accumulation of gut-derived toxins including ammonia[6]

- People with cirrhosis commonly have increased blood ammonia levels which can lead to accumulation in the brain, impairing neurological function[6,8]
- Infections and systemic inflammation also frequently play a role in triggering HE[6]

Development of HE has a negative impact on:

- Patient survival[6,8]
- Patient quality of life[4,9]
- Spouse/caregiver quality of life[4,9]
- Healthcare costs[8]
  - Severe episodes require prolonged hospital admissions and have a greater risk of mortality[3,10]
  - Healthcare costs and resource burden are increasing as the incidence of chronic liver disease and cirrhosis continues to rise whilst the quality of life is reduced[9-12]

Early identification and intervention are key to improving patient outcomes and reducing hospital admissions.[4,13] Under diagnosis and undetected episodes of HE results in delays to optimised treatment[4]

Challenges associated with HE[13]

→ **HE can affect individuals across a broad range of liver diseases not just patients with cirrhosis**

→ **Diagnosis of HE can be difficult**
- Clinical features are not always obvious
- HE is underdiagnosed and undertreated
- Lack of awareness of HE among non-specialists
- No single conclusive test, with diagnosis reliant on clinical suspicion and recognition of features

→ **Current guidelines (EASL and AASLD*) relating to HE have not been updated since 2014**
- Lack of accepted and utilised descriptive and characterisation terms
- Greater emphasis on the importance of nutrition is required
- Requirement for improved care pathways

→ **Need to improve co-ordination of care between primary and secondary care**
- Importance of prophylactic treatment with lactulose and rifaximin-α for patients with recurrent episodes may not be appreciated

→ **Patient and caregiver education is lacking**
- Understanding diagnosis and management
- Recognising early symptoms and escalation of episodes, what to do and whom to contact
- Importance of nutrition – increased protein intake and avoiding periods of fasting
- Compliance with medications

Stop. Think HE. Refer.

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Recognising HE

HE has a wide spectrum of non-specific neurological and psychiatric symptoms[14]

HE should be suspected in patients with cirrhosis, or those with suspected chronic liver disease (malnourishment and sarcopenia) and can be graded[13]

Clinical features and grades[8,13]

1 Minimal lack of awareness, shortened attention span, impairment of calculation ability, reversed sleep-wake cycle

2 Disorientation, lethargy, inappropriate behaviour, personality changes, dyspraxia

3 Reduced conscious level, somnolent but responsive to stimuli, slurred speech

4 Coma, unresponsive to verbal or physical stimulation

1

Risk factors for HE[13]

Several risk factors may precipitate acute episodes of HE and are seen in around 50% of patients admitted

- Constipation
- Infections
- Electrolyte abnormalities
- Dehydration

Drug-related:

- Concomitant opioids
- Proton pump inhibitors
- Benzodiazepines
- Sedatives
- Diuretics

2

Diagnosis of HE[13]

Medical history, risk factors, previous episodes

Neuropsychiatric assessment

Clinical and neurological examination

Laboratory testing: full blood work, ammonia

Imaging for non-specific clinical presentation

Often HE is a diagnosis of exclusion

3

Potential misdiagnosis of HE[13]

- Stroke
- Parkinson's disease
- Delirium
- Intoxication (alcohol or substance abuse)
- Dementia
- Sleep apnoea
- Korsakoff's syndrome
- Wernicke's encephalopathy

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Treatment of HE[13]

- Relevant specialist should be involved within 24-hours of admission
- Grade 1 or low grade 2 HE – managed with safe step intervention using lactulose, referral to hepatology or gastroenterology and patient education
- Early addition of rifaximin, if questioning uncovers overt HE episodes
- Nutritional assessment and referral to dietician is recommended
- Grade 2 or above will require immediate hospital admission and nutritional assessment

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Discharge and ongoing management

- Effective discharge planning and strategies for the ongoing management of HE are essential to reduce recurrent hospital admissions and episodes of HE[13]
- Optimisation of patients' medications should be carried out prior to discharge with titration of lactulose dose. The combination of rifaximin-α and lactulose therapy may significantly reduce the recurrence of HE events and rate of HE related hospitalisations[15,16]
- **A clear discharge care plan to aid coordination of care[13]**
  - Ensure patient/carer and primary care physician understand continued treatment will help reduce episodes of HE and hospitalisation
  - Ensure primary care physician understands resistance is less likely to develop with rifaximin-α than with systemic antibiotics due to local mode of action
  - Information should be provided on how to access specialist services to the patient and carer
- HE is a severe manifestation of cirrhosis so consideration should be given for transplant assessment, if appropriate, or supporting end of life care, if transplant is not appropriate[13]

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Early recognition of HE and prompt referral to specialist care, facilitates effective intervention

A 'better together' approach combining rifaximin-α and lactulose versus lactulose alone, improves patient outcomes, quality of life and reduces the cost burden on the healthcare system by reducing admissions[15,17]

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Recognising HE[9,13]

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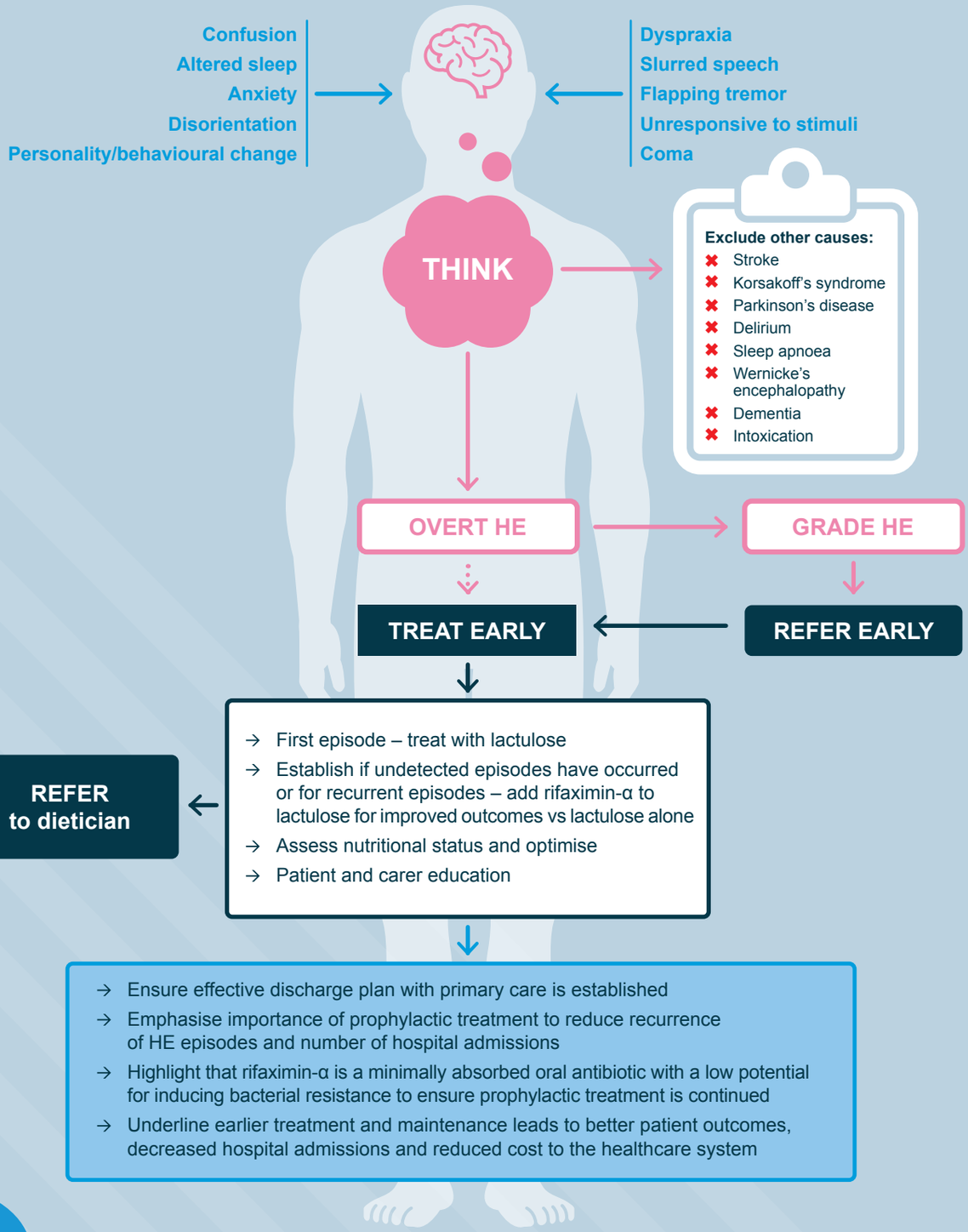

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*EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases

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INTERNATIONAL ABBREVIATED PRESCRIBING INFORMATION: XIFAXAN® / TARGAXAN® 550 mg (rifaximin-α)

Presentation: Blister pack with film-coated, pink tablets containing 550 mg rifaximin for oral administration.

Indication: Reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

Dosage and administration: 550 mg twice a day orally with a glass of water, with or without food. No specific dosing adjustment is necessary for patients with hepatic insufficiency or for the elderly. The safety and efficacy of rifaximin have not been established in paediatric patients under 18 years of age.

Contraindications: Hypersensitivity to rifaximin, rifamycin derivatives or any of the excipients. Cases of intestinal obstruction.

Warnings and 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. Caution should be used in patients with impaired renal function. Concomitant administration of rifaximin with other rifamycins is not recommended. Rifaximin may cause a reddish discolouration of the urine. Use caution in patients with severe hepatic impairment (Child-Pugh C) 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.

Interactions: No experience administering rifaximin to subjects taking another rifamycin antibacterial agent to treat a systemic bacterial infection. *In vitro* data show rifaximin did not inhibit major cytochrome P450 (CYP) drug metabolizing enzymes. Rifaximin did not induce CYP1A2 and CYP2B6 but was a weak inducer of CYP3A4. In healthy subjects studies demonstrated rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however in hepatic impaired patients rifaximin may decrease exposure of CYP3A4 substrates administered concomitantly (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives) due to higher systemic exposure. Increases and decreases in international normalised ratio have been reported in patients on warfarin and rifaximin. Carefully monitor international normalised ratio if co-administration is necessary. Dose adjustments of anticoagulants may be necessary. *In vitro* work suggests rifaximin is a moderate substrate of P-glycoprotein (P-gp) and metabolised by CYP3A4. It is unknown if concomitant drugs which inhibit P-gp and/or CYP3A4 increase systemic exposure of rifaximin. Clinical interaction between rifaximin and compounds that undergo efflux via P-gp and other transport proteins is unlikely (MRP2, MRP4, BCRP and BSEP).

Pregnancy and lactation: No or limited data on the use of rifaximin in pregnant women. Animal studies showed transient effects on ossification and skeletal variations in the foetus. Use of rifaximin during pregnancy is not recommended. It is unknown whether rifaximin/metabolites are excreted in human milk. A risk to the child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy.

Undesirable effects: Adverse effects observed in the placebo-controlled study RFHE3001 and long-term study RFHE3002: Common (>1/100 to <1/10): Depression, dizziness, headache, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia, oedema peripheral. Prescribers should consult country approved Summary of Product Characteristics for further information in relation to undesirable effects.

Overdose: No case of overdose has been reported. In patients with normal bacterial flora, rifaximin in dosages of up to 2,400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage. In case of accidental over-dosage, symptomatic treatments and supportive care are suggested.

Price and pack sizes: PVC-PE-PVDC/Aluminium foil blisters in cartons of 28 or 56 tablets. A 98-tablet carton is also available in some markets. Contact local distributor for price.

Legal category: POM

Prescribing information: Medicinal product subject to medical prescription.

Marketing authorisation holder: Norgine BV, Antonio Vivaldistraat 150, 1083 HP Amsterdam, The Netherlands.

Product licence number: PL20011/0020

ATC code: A07AA11

Date International Prescribing Information prepared: December 2020

Company reference: GL-HEP-XIF-2000207

XIFAXAN®/TARGAXAN® has varying availability and licensing internationally. Before prescribing, consult your country approved prescribing information, available from your local distributor or Norgine Ltd.

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