NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Rifaximin for maintaining remission from episodes of hepatic encephalopathy

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of rifaximin within its licensed indication for the maintenance treatment of hepatic encephalopathy.

Background

Hepatic encephalopathy (also known as portal systemic encephalopathy) is a neuropsychiatric syndrome caused by hepatic insufficiency associated with acute or chronic liver disease. Hepatic encephalopathy is considered to be caused by the body's inability to remove ammonia from the blood stream, and the accumulation of neurotoxins in the blood affects brain function. Hepatic encephalopathy can be classified by causes such as acute liver failure (type A), the presence of portosystemic 'shunt' which allows blood to bypass the liver, without intrinsic liver disease (type B) and cirrhosis of the liver (type C). Signs and symptoms of hepatic encephalopathy include personality changes, intellectual impairment, reduced level of consciousness and altered neuromuscular activity. Hepatic encephalopathy is associated with diminished health related quality of life, impaired daily function, decreased work productivity and frequent hospitalisation for the treatment of acute episodes.

Hepatic encephalopathy can be classified as 'overt' or 'minimal'. Overt hepatic encephalopathy is a condition of neurological and neuropsychiatric abnormalities that can be detected by bedside clinical tests. Overt hepatic encephalopathy can be episodic (also called 'acute') or persistent (also called 'chronic'). Minimal hepatic encephalopathy is a syndrome with a normal mental and neurological status, but specific psychometric tests give abnormal results. Hepatic encephalopathy can be graded using the Conn score (also called West Haven classification) in which higher scores indicate a higher severity, as follows:

- Grade 0: No personality or behavioural abnormality detected.
- Grade 1: lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition.
- Grade 2: lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behaviour, impaired performance of subtraction.
- Grade 3: somnolence to semi stupor but responsive to verbal stimuli, confusion, gross disorientation.
- Grade 4: coma (unresponsive to verbal or noxious stimuli).

Approximately 70% of people with cirrhosis present with subclinical or mild hepatic encephalopathy and 23-40% progress to a more severe form of the disease. The general practice research database (GPRD) estimated the prevalence of hepatic encephalopathy as 1.4 per 100,000 in 2008 in the UK. One and three year survival rates after experiencing an episode of hepatic encephalopathy are 42% and 23% respectively.

Hepatic encephalopathy treatment involves managing acute episodes, and reducing the recurrence of episodes using maintenance treatment. Treatments aim to reduce the production and absorption of ammonia in the gut. Current management of acute episodes of hepatic encephalopathy involve the use of disaccharides (such as lactulose), to convert soluble ammonia to insoluble ammonium, with or without antibiotics (such as neomycin), to inhibit ammonia-generating bacteria. Currently, there are no therapies licensed in the UK specifically for the reduction in risk of recurrence of hepatic encephalopathy episodes. People with hepatic encephalopathy may receive treatment with lactulose to prevent recurrence of hepatic encephalopathy episodes. Long term use of antibiotics is not recommended due to the associated toxicities.

The technology

Rifaximin (Xifaxan; Norgine) is a semi-synthetic derivative of the antibiotic rifamycin, which inhibits ribonucleic acid (RNA). Rifaximin 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. It is administered orally.

Rifaximin does not currently have a UK marketing authorisation for the maintenance of remission from episodes of hepatic encephalopathy. Rifaximin has been studied in clinical trials for the treatment of adults who have had prior episodes of hepatic encephalopathy and are now in remission. Rifaximin has been compared with lactulose and placebo. Concomitant administration of lactulose was allowed in some of the studies.

Intervention(s)	Rifaximin
Population(s)	Adults who have had prior episodes of hepatic encephalopathy and are currently in remission
Comparators	• Lactulose • Neomycin • Neomycin with lactulose
Outcomes	The outcome measures to be considered include: • disease progression to more severe grade of hepatic encephalopathy

	• frequency of hospitalisation, and time until next hospitalisation • frequency of recurrent acute episodes of hepatic encephalopathy and time to next episode • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows, consideration will be given to rifaximin given with or without concomitant medications, such as lactulose. If evidence allows the effectiveness will be assessed by severity of liver failure. Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	None