NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Rifaximin-α for the maintenance of remission from episodes of hepatic encephalopathy

Draft 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 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.

The aim of treatment is to reduce the production and absorption of ammonia in the gut. Current management of acute episodes of hepatic encephalopathy involves the use of antibiotics (such as neomycin) to inhibit ammonia-generating bacteria, and disaccharides such as lactulose to convert soluble ammonia to insoluble ammonium. People with hepatic encephalopathy with low plasma ammonia may receive treatment with lactulose for the prevention of recurrence of acute episodes of hepatic encephalopathy.

The technology

Rifaximin-α (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-α does not currently have a UK marketing authorisation for the maintenance of remission from episodes of hepatic encephalopathy. Rifaximin-α in combination with lactulose has been studied in clinical trials for the treatment of adults with liver cirrhosis who have had prior acute episodes of hepatic encephalopathy compared with lactulose or placebo.

Intervention(s)	Rifaximin-α in combination with lactulose
Population(s)	Adults with liver cirrhosis who have had prior acute episodes of hepatic encephalopathy and are currently in remission
Comparators	• Lactulose • Neomycin
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 • rate of liver transplantation • time to liver transplantation • 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 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

Questions for consultation

Is the population appropriately defined?

Have the most appropriate comparators for rifaximin-α for the maintenance of remission from episodes of hepatic encephalopathy been included in the scope? Are the comparators listed routinely used in clinical practice?

- Should neomycin in combination with lactulose be considered as a comparator?

Are the outcomes suggested appropriate? Given that rifaximin-α does not act directly on the liver, is it appropriate to include the liver transplant outcomes?

Are the subgroups suggested in 'other considerations' appropriate?

- Is rifaximin-α likely to be used to manage hepatic encephalopathy in people with a severe liver failure?

Are there any other subgroups of people in whom rifaximin-α is expected to be more clinically effective and cost effective or other groups that should be examined separately?

- Should severity of hepatic encephalopathy be considered as a subgroup?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the

remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which rifaximin-α will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits