Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Rifaximin for the maintenance treatment of hepatic encephalopathy

Draft scope (Pre-referral)

Draft 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 is a neuropsychiatric syndrome caused by hepatic insufficiency due to acute or chronic liver disease . Symptoms of hepatic encephalopathy are episodic and include personality changes, intellectual impairment, reduced level of consciousness and altered neuromuscular activity. It is also associated with diminished health related quality of life, impaired daily function, decreased work productivity and frequent hospitalisation for the treatment of acute episodes.

In healthy individuals nitrogenous compounds which are generated by bacteria found in the gut are metabolised and excreted by the liver. Hepatic encephalopathy is classified by the underlying cause as type A (acute liver failure), type B (the presence of a portosystemic 'shunt' which allows blood to bypass the liver without intrinsic liver disease) or type C (cirrhosis of the liver). Symptoms of hepatic encephalopathy are caused by an individual's impaired ability to remove ammonia from the blood stream which then crosses the blood brain barrier and affects brain function.

Hepatic encephalopathy is usually diagnosed by a number of investigations, including neuropsychometric tests (such as the psychometric hepatic encephalopathy score), brain imaging and clinical scales (such as the West Haven criteria) after other possible causes of encephalopathy have been excluded. It is graded in order of severity by the degree of confusion and level of consciousness.

Approximately 70% of patients with cirrhosis present with subclinical or mild hepatic encephalopathy, and 23-40% may 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 population 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 which often require hospitalisation involves the use of antibiotics (such as neomycin and metronidazole) to inhibit ammonia-generating bacteria, and disaccharides such as lactulose to convert soluble ammonia to insoluble

ammonium. Plasma levels of ammonia are then decreased and the symptoms of hepatic encephalopathy are minimised. People with hepatic encephalopathy with low plasma ammonia may receive maintenance treatment with lactulose to reduce the recurrence of acute episodes.

The technology

Rifaximin (Xifaxan; Norgine and Alfa Wassermann) 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 treatment of hepatic encephalopathy. Rifaximin has been studied in clinical trials as monotherapy or in combination with lactulose for the treatment of adults with liver disease who have had prior acute episodes of hepatic encephalopathy (grade II-IV) compared with lactulose or placebo.

Intervention(s)	Rifaximin
Population(s)	Adults who have had prior acute episodes of hepatic encephalopathy
Comparators	Lactulose
Outcomes	The outcome measures to be considered include: • disease progression to more severe grade of hepatic encephalopathy • frequency of hospitalisation • frequency and severity of recurrent acute episodes of hepatic encephalopathy • 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	Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Guidelines: Clinical Guideline No. 100 June 2010, 'Alcohol use disorders: Physical complications'

Questions for consultation

Has the most appropriate comparator for rifamixin for the maintenance treatment of hepatic encephalopathy been included?

Are there any other treatments which are routinely used in the UK to delay the recurrence of acute episodes of hepatic encephalopathy?

Is rifaximin intended to be used for the maintenance treatment of all types (that is, types A, B and C) and grades of hepatic encephalopathy?

Should rate of liver transplantation be included as an outcome measure?

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

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

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.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)