NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Rifaximin-α for maintaining remission from episodes of hepatic encephalopathy

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Current practice

- The final scope for this appraisal specifies rifaximin-α as the intervention, but the manufacturer's base-case economic analysis assessed rifaximin-α plus concomitant lactulose. The manufacturer stated that this was in line with current UK clinical practice and that the SPC highlights that lactulose was used concomitantly in the pivotal trial. What is the Committee's view on how rifaximin-α will be used in clinical practice? Will it be prescribed for the duration of the disease?
- The manufacturer excluded neomycin from the analyses presented in its submission on the basis that it is not commonly used in clinical practice for preventing long-term hepatic encephalopathy recurrence, is associated with adverse events, and it is not licensed for this indication. What is the Committee's view on the current use of neomycin for the treatment of hepatic encephalopathy in the UK? Is it used for maintenance of remission from hepatic encephalopathy?
- What is the Committee's view on the validity of the Conn score and Asterixis grade for diagnosing an episode of hepatic encephalopathy?

- What treatment is given to patients receiving rifaximin in combination with lactulose who are admitted to hospital to treat an episode of hepatic encephalopathy? Can another antibiotic be given if patients are already taking rifaximin?

Clinical effectiveness

- Does the Committee consider the manufacturer's review of the literature to be complete given the ERG's concern that some records may have been omitted as a result of the use of the search term 'rifaximin-α' which was not as sensitive as the term 'rifaximin' used in the initial search?
- What is the Committee's view on the generalisability of the trial to the UK population and clinical practice given that:
  - The population in the trial and manufacturer's submission includes only people with hepatic encephalopathy associated with chronic liver disease and with a Model End Stage Liver Disease (MELD) score of 25 or less.
  - A mean dose of lactulose of 3.14 cups daily for the rifaximin-α group and 3.51 cups daily for the placebo group (equivalent to 47 ml and 53 ml daily) was used in the RFHE3001 trial and the manufacturer's economic model rather than the licensed dose of 30 ml to 50 ml 3 times daily (90 ml to 150 ml daily).
- What is the Committee's view on the use of rifaximin alone compared with placebo in maintaining remission from episodes of hepatic encephalopathy?
- Rifaximin in combination with lactulose decreased hospitalisation compared to lactulose alone. Is there data on the duration of the hepatic encephalopathy episode or length of hospital stay for rifaximin in combination with lactulose compared with lactulose alone?
- Is there evidence for oral antibiotics or non-absorbable disaccharides in improving mortality in patients with hepatic encephalopathy that is secondary to chronic liver disease?

Cost effectiveness

- The ERG noted that approximately 10% of the patients in the economic model were still alive at the end of the 5-year time horizon. It stated that clinical opinion suggests that these were likely to be people with stable liver disease and

considered this time horizon to be appropriate. Does the Committee consider the manufacturer's use of a 5-year time horizon to be appropriate?

- What is the Committee's view on the distributions used in extrapolation of the clinical outcomes (base case and sensitivity analyses) given the ERG's concern that some of the manufacturer's methods and assumptions were not adequately justified?
- What is the Committee's view on the manufacturer's use of the combined dataset from the RFHE3001 and RFHE3002 studies to fit the rifaximin-α arm of the model, while only the RFHE3001 data was used to fit the placebo arm of the model?
- What is the Committee's view on the manufacturer's assumption of constant probability of subsequent hepatic encephalopathy episodes over time, given the ERG's concern that this may not be reflective of real life?
- The ERG stated that the mortality risks assumed for Conn score categories 3 (53.86%) and 4 (71.89%) may have been overestimated, based on clinical expert opinion, and when these were reduced to lower values the ICER increased. What is the Committee's view on the mortality risks estimated for these Conn score categories by manufacturer?
- What is the Committee's view on the appropriateness and reliability of the source of data used to derive the mortality risks in the economic model?
- What is the Committee's view of the appropriateness of the source of data used to derive the utility estimates in the economic model?
- Does the Committee consider that the costs of adverse events should be included in the model?
- What is the Committee's view on the subgroup analyses conducted by the manufacturer, given that this was not based on a pre-planned subgroup from the RFHE3001 trial or a formal post-hoc subgroup and the number of people who did not receive concomitant lactulose (subgroup B) was small (8.7% of patients in the RFHE3001 trial).
- Does the Committee accept the ERG's exploratory analyses, including the adjustments to the model parameters? Which ICER does it consider to be the most plausible?

1 Background: clinical need and practice

1.1 Hepatic encephalopathy is a neuropsychiatric syndrome caused by the body's inability to remove ammonia from the blood stream usually associated with acute or chronic liver disease, but most commonly with liver cirrhosis. This leads to accumulation of neurotoxins in the blood which affects brain function. Symptoms of hepatic encephalopathy include personality changes, intellectual impairment, reduced level of consciousness and altered neuromuscular activity. It is associated with diminished health-related quality of life, impaired daily function, decreased work productivity and frequent hospital admission for treating acute episodes. Hepatic encephalopathy can be classified as minimal or overt. Minimal hepatic encephalopathy is a syndrome with normal mental and neurological status, but with specific psychometric tests indicating abnormalities (remission stage). Overt hepatic encephalopathy is associated with clinically relevant neurological and neuropsychiatric abnormalities detected by bedside clinical tests and can be acute or chronic. It is graded using the Conn score (also called West Haven classification) on a scale of 0 (no personality or behavioural abnormality detected) to 4 (coma). Minimal hepatic encephalopathy includes Conn scores 0 and 1, while Conn scores 2 to 4 are classed as overt hepatic encephalopathy.

1.2 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 manufacturer estimated, based on data for cirrhosis, that approximately 23,000 people in England and Wales would present with minimal hepatic encephalopathy and between 5400 and 9400 people would progress to overt hepatic encephalopathy and therefore be eligible for treatment. The 1 and 3-year survival rates after experiencing hepatic encephalopathy are 42% and 23% respectively. People who have had 1 episode of hepatic encephalopathy are at a risk of developing episodic recurrences, even in the absence of known precipitating factors. Most people with symptomatic chronic liver disease

will experience progressive deterioration of liver function, further reducing the liver's ability to deal with toxins and increasing the likelihood of further episodes of hepatic encephalopathy.

1.3 Hepatic encephalopathy treatment involves managing acute episodes, and reducing the recurrence of episodes using maintenance treatment. Treatment aims to reduce the production and absorption of ammonia in the gut. Current pharmacological management of hepatic encephalopathy involve using 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 recommended by NICE for maintaining remission from episodes of hepatic encephalopathy. People with hepatic encephalopathy may receive lactulose to prevent recurrence of hepatic encephalopathy episodes. Long term use of antibiotics is not recommended due to the associated toxicities.

2 The technology

2.1 Rifaximin-α (Targaxan, Norgine) is a semi-synthetic derivative of the antibiotic rifamycin, which inhibits ribonucleic acid (RNA). Rifaximin-α 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. Rifaximin-α has UK marketing authorisation 'for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients aged 18 years or older'. The summary of product characteristics highlights that 91% of the patients in the pivotal study were using concomitant lactulose.

2.2 The summary of product characteristics lists the following adverse reactions for rifaximin-α: depression, dizziness, headache, dysponea, abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia, anaemia, oedema

peripheral and pyrexia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Rifaximin-α is available as 550 mg film-coated tablets at a net price of £259.23 per 56-tablet pack (excluding VAT; 'Medicines Index of Medicinal Specialties [MIMS]). It is administered orally at a recommended dose of 550 mg twice daily. The manufacturer estimated an average cost of £1689.65 for 6 months of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal is to appraise the clinical and cost effectiveness of rifaximin within its licensed indication for the maintenance treatment of hepatic encephalopathy.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults who have had prior episodes of hepatic encephalopathy and are currently in remission	Adults with chronic liver disease who have had prior episodes of overt hepatic encephalopathy and are currently in remission

The manufacturer stated that the indication and submission does not cover patients with hepatic encephalopathy which is caused by an acute liver insult. In addition to the exclusion of hepatic encephalopathy due to acute liver disease, the ERG stated that patients with more severe liver disease (MELD score of 25 or more) were also excluded from the analysis. However, it noted the manufacturer's assertion that the results would be applicable to this population as well. The ERG was concerned about the validity of this assumption, given that the treatment effect of rifaximin-α compared with placebo was not statistically significant in the subgroup with MELD scores of 19 to 24 (the more severe MELD score category in the trial). In addition, it noted that the study by Hassest et al. 2001 which was provided as evidence for the effectiveness of rifaximin-α in patients with MELD scores of 20 or more was a poor quality descriptive study.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Rifaximin	Rifaximin plus concomitant lactulose (as per ITT population in RFHE3001)

The manufacturer stated that the economic analysis of rifaximin-α included the use of concomitant lactulose based on data from the RFHE3001 trial where 91.3% of patients received lactulose in both treatment arms. It also stated that rifaximin-α will be administered concomitantly with lactulose in clinical practice in the majority of cases. Results for rifaximin alone compared with placebo were presented as a subgroup analysis. The ERG stated that their clinical expert agreed that UK current practice involved using concomitant lactulose.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	• Lactulose • Neomycin • Neomycin with lactulose	Placebo plus concomitant lactulose (as per ITT population in RFHE3001)

The manufacturer stated in the clarification response that rifaximin-α plus concomitant lactulose was compared with lactulose alone (termed ‘placebo’ in the submission). The manufacturer stated that neomycin is not commonly used in clinical practice for preventing long-term hepatic encephalopathy recurrence, no clinical data is available for the use of neomycin in this indication, it is associated with risks of ototoxicity, nephrotoxicity and hepatic impairment and also does not have a license for this indication. The manufacturer also stated that the only trial comparing rifaximin-α with neomycin was not considered appropriate for this appraisal in terms of the population, treatment regimens and outcomes, and the ERG acknowledged these limitations. However, the ERG stated that although neomycin is not as well tolerated as rifaximin-α, clinical expert opinion indicated that it works through the same process as rifaximin-α and is sometimes used in clinical practice, especially in people who cannot undergo liver transplantation.

	Final scope issued by NICE	Decision problem addressed in the submission
Outcomes	• 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 evaluation	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.	

3.2 Rifaximin-α is proposed as an add-on therapy to existing management of hepatic encephalopathy for people who are in remission from episodes of hepatic encephalopathy.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a systematic literature review and identified 3 relevant studies including rifaximin-α. Of these, the submission excluded 2 studies due to difference in doses from the UK marketing authorisation for rifaximin-α. The submission therefore included 1 study (Bass et al., 2010) which reported results from the pivotal trial – RFHE3001. This was a 6 month international, multicentre, randomised, double-blind, placebo-controlled trial comparing rifaximin-α with placebo for maintaining remission in people with recurrent, overt, episodic hepatic encephalopathy resulting from chronic liver disease. Patients receiving lactulose at baseline and were allowed to continue using it throughout the study period. The manufacturer also conducted a review of unpublished data available on its database and identified a second trial – RFHE3002. This

was an international, multicentre, single-arm, open-label study which assessed the long-term safety and tolerability of rifaximin-α in patients with a history of hepatic encephalopathy. It was an extension to RFHE3001 and patients who successfully completed the RFHE3001 study were eligible to participate, in addition to new patients. The manufacturer stated that interim results of this study had been presented as abstracts and no peer review publications were available at the time of the evidence submission to NICE.

RFHE3001 trial

4.2 Patients were considered eligible to participate in the RFHE3001 study if they had a Conn score of 0 or 1 and were in remission after 2 or more documented recurrent episodes of overt hepatic encephalopathy associated with cirrhosis or portal hypertension equivalent to a Conn score of 2 or more within 6 months prior to screening. Patients were only considered eligible if they had a MELD score of less than 25, therefore patients with more severe liver disease (MELD score of 25 or more) were excluded from the study. After screening, 299 patients were randomised to receive either 550 mg of rifaximin-α (n=140) or matching placebo (n=159) twice daily, in addition to on-going treatment with lactulose. In the rifaximin and placebo groups, 91.4% and 91.2% of patients took concomitant lactulose during the course of the study respectively. The mean duration of treatment was 130.3 days in the rifaximin-α group and 105.7 days in the placebo group. The rate of compliance, defined as use of at least 80% of dispensed tablets, was high in both treatment groups (84.3% in the rifaximin-α group and 84.9% in the placebo group). Patients discontinued treatment if they experienced an adverse event with an unacceptable risk to them, developed any condition fulfilling the exclusion criteria, experienced a breakthrough overt hepatic encephalopathy episode, became pregnant or requested to be withdrawn.

4.3 Baseline patient characteristics were generally similar between the 2 treatment groups. The mean age was approximately 56 years (81% of the

participants were less than 65 years), 86% were white and 60.9% were male (54% in the rifaximin-α group and 67% in the placebo group). Baseline Conn score and asterixis grade were 0 for most patients (67% and 68% respectively). There were no notable differences between the treatment groups in terms of disease history.

4.4 The primary outcome in the RFHE30001 trial was the time to the first breakthrough overt hepatic encephalopathy episode, defined as an increase in the Conn score from 0 or 1 to 2 or more or an increase in Conn and asterixis score of 1 grade each for those patients who entered the study with a Conn score of 0. The Conn score detects the severity of impaired mental status in overt hepatic encephalopathy according to 4 progressive stages (0 to 4, with higher scores indicating more severe impairment). The asterixis grade detects worsening neurological impairment according to the flapping tremor which is determined by the patient extending their arms with wrists flexed backwards and fingers open for 30 seconds or more. This is also measured on a scale of 0 to 4, with higher scores indicating more flapping motions. Key secondary outcomes included time to first hepatic encephalopathy-related hospital admissions, time to any increase from baseline in Conn score, time to any increase from baseline in asterixis grade, mean change from baseline in fatigue domain score on the Chronic Liver Disease Questionnaire (CLDQ) at end of treatment and mean change from baseline in venous ammonia concentration at end of treatment. The CLDQ was used by the patients to measure their level of fatigue on a 7-point scale, with ‘1’ representing a high degree of fatigue and ‘7’ representing minimal fatigue. Results were based on the ITT population, that is, all randomised patients who received at least one dose of the study drug.

4.5 There was a statistically significant reduction in the risk of a breakthrough episode by 58% with rifaximin-α compared with placebo during the 6-month study period, with a hazard ratio (HR) of 0.42 (95% confidence interval [CI] 0.28 to 0.64, $p<0.001$). This was based on 31 patients

(22.1%) in the rifaximin-α group experiencing an overt breakthrough episode during the study compared with 73 patients (45.9%) in the placebo group. Patients who terminated early for reasons other than breakthrough overt hepatic encephalopathy were contacted at 6 months from randomisation to determine if they had experienced a breakthrough overt hepatic encephalopathy episode. The manufacturer stated that therefore breakthrough overt hepatic encephalopathy episodes were captured completely for up to 6 months post randomisation. Patients who did not experience an overt breakthrough episode during the study period were followed-up and assessed after the study was discontinued. The results were similar to the 6-month study period, with a hazard ratio for a breakthrough episode of 0.46 (95% CI 0.31 to 0.69, p<0.0001).

4.6 Age, MELD score, duration of current verified remission and number of prior hepatic encephalopathy episodes were identified as significant prognostic factors and to control for these factors due to chance imbalances between treatment groups, multivariate analysis was performed using the Cox proportional hazards model. This resulted in a statistically significant reduction in the risk of an overt breakthrough hepatic encephalopathy episode during the course of the study (HR 0.40, 95% CI 0.26 to 0.62, p<0.0001) with rifaximin-α.

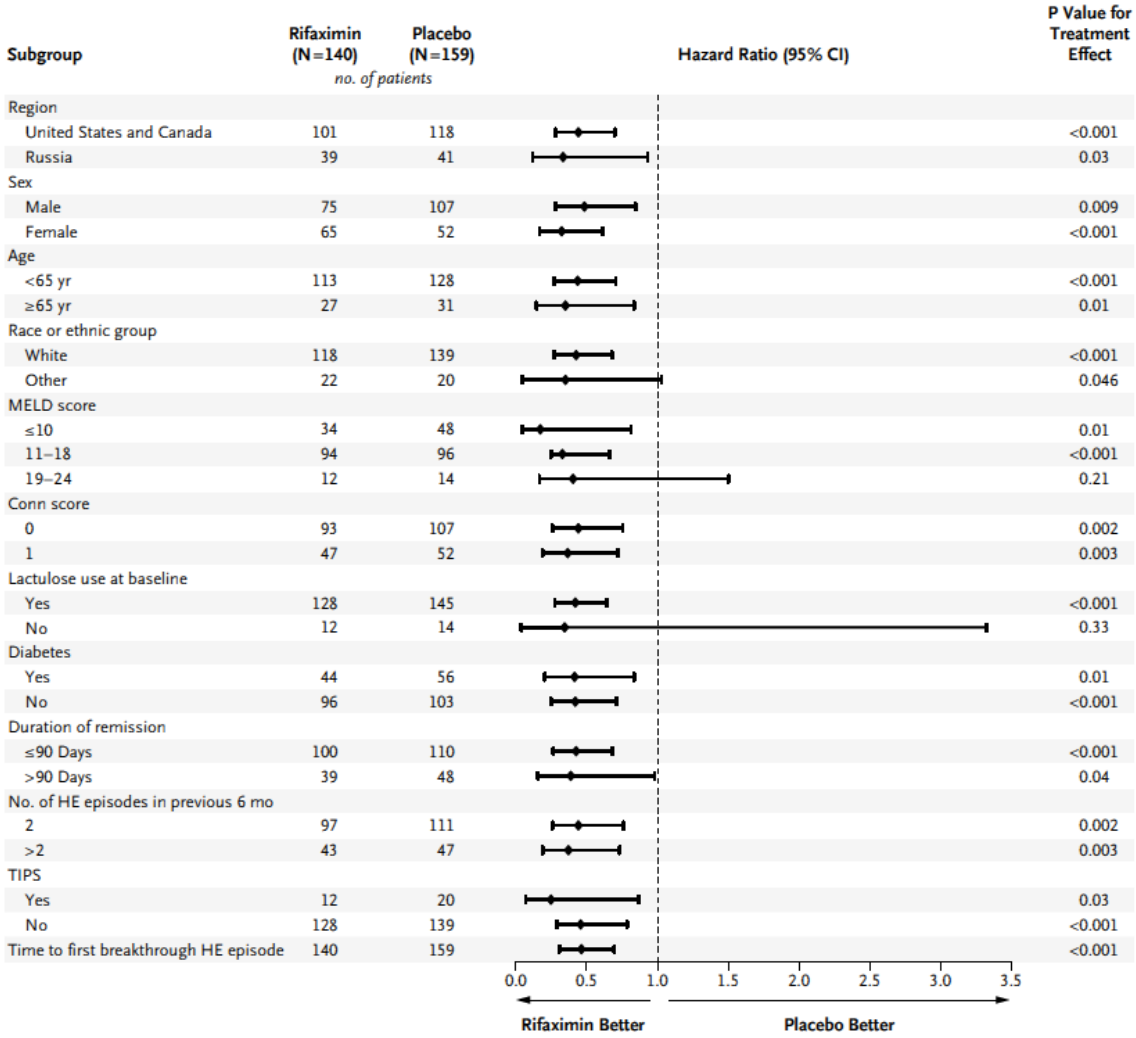
4.7 The manufacturer carried out a sensitivity analysis of the primary outcome to exclude patients with comorbid conditions such as constipation, analgesic use, infection and portal shunt surgery. This results indicated statistically significant risk reductions of overt breakthrough episodes in patients with comorbid conditions (HR 0.25, 95% CI 0.11 to 0.57, p=0.0004) and patients without comorbid conditions (HR 0.51, 95% CI 0.31 to 0.84, p=0.0068). The manufacturer also presented another sensitivity analysis which excluded patients who took concomitant medications. This also resulted in a statistically significant reduction in the risk of an overt break through episode with rifaximin-α compared with placebo (HR 0.42, 95% CI 0.28 to 0.64, p<0.0001).

4.8 Rifaximin-α was shown to be associated with statistically significant reductions compared with the placebo for the secondary outcomes of hepatic encephalopathy-related hospital admissions (HR 0.50, 95% CI 0.29 to 0.87, p=0.01) and time to any increase from baseline in Conn score (HR 0.46, 95% CI 0.31 to 0.69, p<0.0001). However, the reduction in time to any increase from baseline in asterixis grade with rifaximin-α did not reach statistical significance when compared with placebo (HR 0.65, 95% CI 0.41 to 1.01, p=0.0523). The difference in the changes from baseline in CDLQ fatigue scores were minimal (3.28 compared with 3.34 at baseline and 3.57 compared with 3.51 at the end of treatment for the rifaximin-α and placebo groups respectively). The manufacturer stated that this was because patients were not able to complete the CLDQ assessment during an overt breakthrough hepatic encephalopathy episode due to altered mental and neuromotor status. Therefore, the CLDQ results for these patients would be similar to baseline levels because mental status was closer to baseline levels at the time of end of treatment assessments. The rifaximin-α group had greater reductions in venous ammonia levels compared with the placebo groups, although the difference was not statistically significant (p=0.0818). The manufacturer stated that the mortality data from the trial was not mature enough to address the impact of rifaximin-α on survival.

4.9 Pre-planned subgroup analyses of the primary outcome were evaluated according to geographic region, age, sex, race or ethnic group, baseline Model End Stage Liver Disease (MELD) score, baseline Conn score, diabetes at baseline, duration of current verified remission, number of episodes of hepatic encephalopathy within the 6-months period before randomisation, lactulose use at baseline, and previous placement of a transjugular intrahepatic portosystemic shunt. The effect of rifaximin-α in reducing the risk of overt breakthrough hepatic encephalopathy episodes during the 6-month study period was consistent across the pre-defined subgroups, although the effect was not statistically significant in the subgroup with MELD scores of 19 to 24 (p=0.21) and the subgroup that

did not receive lactulose at baseline (p=0.33). The subgroup results are shown in figure 1.

Figure 1 Results of the subgroup analysis: Study RFHE3001



Abbreviations: HE, hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt. Hazard ratios for the risk of a breakthrough episode of HE during the 6-month study period are shown for the rifaximin group, as compared with the placebo group, for various subgroups. The MELD score can range from 6 to 40, with higher scores indicating more severe disease. The Conn score can range from 0 to 4, with higher scores indicating more severe impairment. The p-values were calculated by means of the log-rank test. Race or ethnic group was self-reported

Source: manufacturer's submission (figure 6, page 51)

4.10 The safety population (n=299) was described by the manufacturer as patients who received at least 1 dose of study drug and provided at least 1 post-baseline safety assessment. About 80% of patients in the rifaximin-α groups and 79.9% in the placebo group experienced adverse events

during the study. The majority of adverse events were mild or moderate. Severe adverse events such as anaemia, ascites, abdominal pain, oesophageal varices and hepatic cirrhosis occurred in 26.1% of patients in the rifaximin-α group compared with 30.8% in the placebo group. Treatment-related adverse events occurred in 19.3% of patients in the rifaximin-α group compared with 21.4% in the placebo group. The most common treatment-related adverse events were diarrhoea (3.6% rifaximin-α compared with 6.9% placebo) and nausea (2.9% rifaximin-α compared with 7.5% placebo). About 11.4% of patients in the rifaximin-α group and 21.4% in the placebo group) had overt breakthrough hepatic encephalopathy episodes which were considered as serious adverse events (for example, due to hospitalisation). A total of 10 patients in the rifaximin-α group and 11 patients in the placebo group died during the study, mainly due to conditions associated with disease progression, including hepatic cirrhosis, decompensated liver cirrhosis or hepatic failure. Adverse events leading to study discontinuation occurred in 21.4% of patients in the rifaximin-α group compared with 28.3% of patients in the placebo group. The manufacturer stated that the majority of the study discontinuations from adverse events were due to hepatic encephalopathy events. Adverse events of special interest based on known potential side effects of systemic antibiotics and prior experience with rifaximin-α occurred similarly between the treatment groups, with diarrhoea being the most common (10.7% with rifaximin-α and 13.2 % with placebo).

RFHE3002 trial

4.11 A total of 322 patients were enrolled to participate in the RFHE3002 single-arm, open label study. Of these, 152 rolled over from the RFHE3001 study (70 patients from the rifaximin-α group and 82 from the placebo group) and 170 patients were newly enrolled. All the participants had a Conn score of 0 to 2 at enrolment and the newly enrolled patients had 1 or more verifiable hepatic encephalopathy episode within 12 months prior to screening. All patients received 550 mg of rifaximin-α

twice daily and were followed up for at least 24 months during which time treatment was still on-going on an out-patient basis or until regulatory approval of rifaximin-α or until the sponsor closed the study, whichever came first. All concomitant drugs including those from the RFHE3001 study were maintained at stable doses wherever possible. The conditions for study discontinuation were the same as those for the RFHE3001 trial, although patients who experienced an episode of recurrent hepatic encephalopathy during the study were not automatically withdrawn as in RFHE3001 and were allowed to continue on medication.

4.12 The new rifaximin-α patients (including newly enrolled patients and placebo group from RFHE3001) and continuing rifaximin-α patients had similar characteristics in terms of [redacted]. Most patients had baseline Conn scores of either 0 (66%) or 1 (30%) and asterixis grades of 0 (71%) or 1(24%). The time since the most recent verified hepatic encephalopathy episode was shorter in the new rifaximin-α group ([redacted]) compared with the continuing rifaximin-α group ([redacted]). The two groups of patients were also different in terms of the number of hepatic encephalopathy episodes experienced prior to screening for RFHE3002 due to the differences in the number of hepatic encephalopathy episodes required for inclusion in the 2 studies. [redacted].

4.13 The efficacy outcomes assessed were change from baseline in Conn scores and asterixis grades over time. [redacted]

[redacted]. The manufacturer stated that the time to first breakthrough overt hepatic encephalopathy episode profiles demonstrated long-term maintenance of remission in new rifaximin-α and continuing rifaximin-α patients. In addition, 60 rifaximin-α patients from RFHE3001 who did not experience a HE episode were followed during RFHE3002 the incidence of breakthrough HE episodes for these patients was lower than that in the RFHE3001 placebo group, after adjusting for exposure time. The manufacturer also stated that the all-cause hospitalisation rate was similar to that observed for rifaximin-α during the shorter double-blind trial. However, hazard ratios were not presented.

4.14 A total of 300 patients (93.2%) reported an adverse event in the RFHE3002 study.

[redacted]. Approximately 56% of patients receiving rifaximin-α experienced severe adverse events,

[redacted]. Overall, 67 deaths occurred during the study or within 30 days after the last dose of rifaximin-α and 8 additional patients died more than 30 days after. The manufacturer stated that none of these deaths were related to rifaximin-α.

[redacted]

Evidence Review Group comments

4.15 In response to clarification, the manufacturer submitted additional searches run at a later date than in the original submission. The ERG considered these updated searches to be the main searches for this appraisal, given that they were the most up-to-date searches and also overlapped the first searches. The ERG stated that the manufacturer's use of the search term 'rifaximin-α' in the second search rather than 'rifaximin' which was used in the first search may have resulted in some studies being omitted. It noted, however, that both search terms returned identical results in the MEDLINE and EMBASE databases although the second search (using 'rifaximin-α') did not work properly in the Cochrane Library. The ERG was aware that the Cochrane Library was largely populated with records from the MEDLINE and EMBASE databases, meaning that there was only a slight probability of some records being omitted in the second search. In general, the ERG stated that it was likely that the systematic review contained all the relevant studies. The ERG identified a 6 month trial of rifaximin compared with neomycin reported by Miglio et al. 1997 which was not presented in the manufacturer's submission. In its clarification response, the manufacturer stated that this trial had been identified but excluded because it was not considered appropriate for this appraisal in terms of the population, treatment regimens and outcomes included. The ERG acknowledged the manufacturer's justification for excluding the study, although it used this study in a scenario analysis for illustrative purposes.

4.16 The ERG stated that the evidence submitted by the manufacturer generally reflects the decision problem adequately even though the population and comparator differed from those specified in the final scope. While the scope referred to adults who have had prior episodes of hepatic encephalopathy, the manufacturer's submission only considered adults with chronic liver disease, excluding hepatic encephalopathy caused by acute liver disease. Patients with more severe liver disease (MELD score of 25 or more) were also excluded from the analysis. However, the ERG

noted the manufacturer's assertion that the results would be applicable to this population as well. The ERG was concerned about the validity of this assumption, given that the treatment effect of rifaximin-α compared with placebo was not statistically significant in the subgroup with MELD scores of 19 to 24 (the more severe MELD score category in the trial). In addition, it noted that the study by Hassest et al. 2001 which was provided as evidence for the effectiveness of rifaximin-α in patients with MELD scores of 20 or more was a poor quality descriptive study. The final scope referred to a comparison of rifaximin-α with lactulose, neomycin or neomycin in combination with lactulose, but the ERG noted that the analysis presented by the manufacturer was based on rifaximin-α in combination with concomitant lactulose compared with placebo in combination with lactulose, in line with the pivotal clinical trial and UK clinical practice. The ERG stated that their clinical expert agreed that UK current practice involved using concomitant lactulose.

4.17 The ERG indicated that the quality of the RFHE3001 trial was high. It considered that the trial randomisation was carried out properly and that the treatment allocation was adequately concealed. It noted that the treatment groups were similar in terms of patient characteristics, although they were more males in the placebo group (67%) than in the rifaximin-α group (54%). The ERG stated that the outcomes assessed were appropriate and in line with those measured in the RFHE3001 and RFHE3002 trials as well as those specified in the scope. Overall, the ERG considered the clinical effectiveness data and the statistical approaches in the manufacturer's submission to be of good validity, although it recognised that the RFHE3002 trial was an unpublished study and did not provide treatment effect data.

5 Comments from other consultees

5.1 Consultees stated that the diagnosis of hepatic encephalopathy is difficult, especially in the early stages, and there are currently no guidelines for managing it in the NHS. It was noted that the majority of patients are

managed within the hospital setting, usually after the first presentation of an overt episode. The Clinical specialist indicated that a large proportion of patients with an overt episode will become comatose and only 52% of this cohort survived their intensive care stay and only 38% survived to hospital discharge, with 15% going on to be transplanted. Consultees emphasised the adverse effects of antibiotics such as neomycin and the clinical specialist stated that neomycin was not an appropriate comparator for the appraisal of rifaximin-α because it is no longer used in clinical practice. While there was general agreement that lactulose is used in clinical practice, the clinical specialist stated that lactulose is poorly tolerated as it induces diarrhoea and bloating. The professional group, however, stated that laxatives such as lactulose are currently used and well accepted for managing hepatic encephalopathy.

5.2 Consultees stated that there was good evidence that rifaximin-α is effective in maintaining remission from episodes of hepatic encephalopathy, with no significant side effects except for nausea. The clinical specialist stated that experience in practice has shown that it results in reduced disability, reduced hospital admissions, improved quality of life and also reduced the burden on carers. The clinical specialist also highlighted that increased levels of the anti-inflammatory cytokine IL-10 were found in the rifaximin-treated group which may allude to its mechanism of action being an anti-inflammatory rather than ammonia-lowering in nature. It was noted that rather than decreasing gut ammonia production, rifaximin may alter the make-up of the gut microbiome resulting in reduced bacterial translocation and endotoxemia and lowering inflammation within the bloodstream. Consultees considered that rifaximin-α would be initiated in secondary care and continued in primary care. No additional costs or training was deemed necessary to use rifaximin-α in clinical practice. The clinical specialist indicated that rifaximin-α treatment should be discontinued if no improvement is observed 4 weeks after starting treatment and also stated that rifaximin is used both as monotherapy and in combination with lactulose.

5.3 Comments from the patient expert stressed that rifaximin-α would provide relief from the effects of hepatic encephalopathy, increase the patients' sense of well-being and improve their quality of life as well that of carers. Potential side effects of rifaximin-α treatment were considered to be more tolerable than the physical and psychological side effects associated with current treatments (such as diarrhoea associated with lactulose), which have a devastating effect on quality of life for the patients and carers. The patient expert therefore re-emphasised the need for inclusion of rifaximin-α as part of the treatment plan for hepatic encephalopathy.

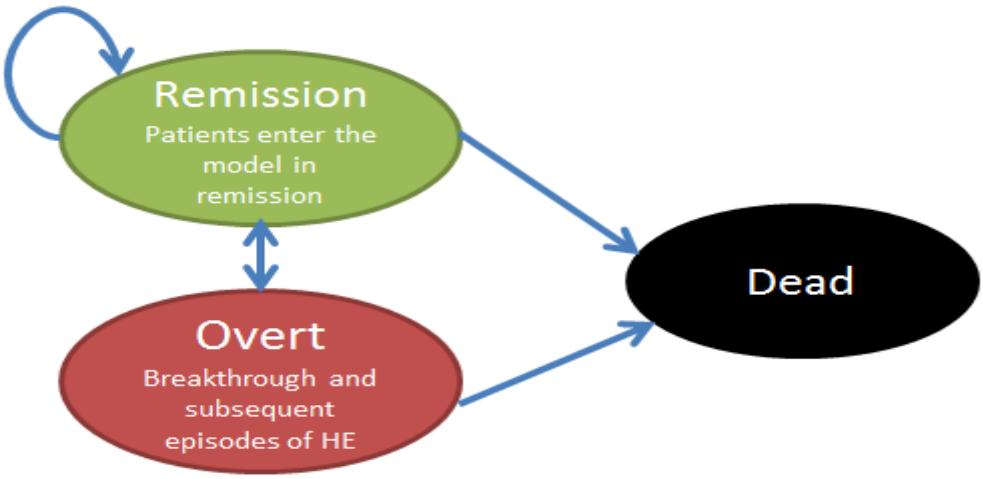
6 Cost-effectiveness evidence

6.1 The manufacturer conducted a systematic review of the literature and identified 1 study in its original submission, followed by 2 additional studies identified as part of the updated search conducted in response to clarification. The manufacturer, however, stated that these were not considered to be relevant as the patient population and outcomes did not match those of the current decision problem. The manufacturer stated that a comparison with neomycin was excluded because it is not routinely used in clinical practice, no clinical data is available for the use of neomycin in this indication, it is associated with risks of ototoxicity, nephrotoxicity and hepatic impairment and it is also not licensed for the indication being appraised.

6.2 The manufacturer carried out a de novo analysis of the cost effectiveness of rifaximin-α plus concomitant lactulose compared with placebo plus concomitant lactulose, given that approximately 91% of patients in each arm of the RFHE3001 trial received concomitant lactulose. A Markov cohort model consisting of 3 states (remission, overt and dead) was developed to reflect the clinical pathway of hepatic encephalopathy (see figure 2). All patients enter the model in the remission state at a mean age of 56.2 years which is consistent with the mean age in the RFHE3001 trial. In each cycle, patients can remain in remission, progress to the overt state (breakthrough and subsequent episodes which may include hospital

admissions), return to the remission state from the overt state or progress to the dead state from the remission or overt states. The model had a time horizon of 5 years consisting of monthly cycles, did not include a half-cycle correction, and both costs and benefits were discounted at 3.5%. The analysis was performed from the perspective of the NHS and personal social services.

Figure 2 Model structure



Source: manufacturer's submission (figure 15, page 94)

6.3 Transition probabilities between the remission and overt states in the model were derived from survival functions based on time-to-event data from the RFHE3001 trial. Time to first breakthrough hepatic encephalopathy episode was extracted and combined from the Kaplan-Meier survival curves in the RFHE3001 and RFHE3002 studies and was used to estimate the proportion of patients in the remission and overt states for the rifaximin-α group in the first 6 months. Data from the RFHE3001 study only was used for the placebo group. The survival curves were then extrapolated beyond the 6 months observation period for both groups using a log-normal distribution which provided the best model fit based on Akaike information criteria (AIC), Bayesian information criteria (BIC) and visual inspections.

6.4 Given that time to subsequent episodes was not available from RFHE3001, the manufacturer assumed that the risk of experiencing a subsequent overt episode was independent of the risk of preceding episodes and the time spent in the remission state. It also assumed that the risk reduction for the first breakthrough episode could also be applied to subsequent episodes, based on clinical expert opinion, and this was assumed to be constant over time for subsequent episodes. Therefore, data on time to first breakthrough episode was used to model the probability of subsequent episodes and this was extrapolated to 5 years using an exponential distribution. The hazard ratio for rifaximin-α compared with placebo was then estimated from the resulting coefficient parameters and applied to the baseline survivor function (placebo) to estimate the survivor function for rifaximin-α.

6.5 The baseline mortality in the model was a combination of all-cause mortality and hepatic encephalopathy-specific mortality. The manufacturer estimated the risk of all-cause mortality based on the age-related life table data for England and Wales from the Office for National Statistics. This risk was adjusted for sex, based on the ratio of males to females in the RFHE3001 trial. Hepatic encephalopathy-specific mortality was estimated from other external data sources (Bustamante et al. 1999 and Shawcross et al. 2011) rather than the RFHE3001 data. The manufacturer stated that this was because the trial population does not reflect the range of patients who would present with hepatic encephalopathy in clinical practice. In addition, patients who experience hepatic encephalopathy were considered to be at a higher mortality risk than patients without it and there was an increased risk of mortality associated with patients' underlying liver disease. The manufacturer stated that data from the trial was not sufficiently mature to for an analysis of mortality. The data from Bustamante et al. showed the survival curve up to 48 months for cirrhotic patients who developed hepatic encephalopathy. This data was extrapolated for 5 years using the log-normal distribution which provided the best model fit based on AIC, BIC and visual inspection and time-

dependent probabilities over 5 years were estimated using the formula in Briggs 2006. The mortality risk at each level of Conn score was based on clinical expert opinion and a publication by Shawcross et al. 2011.

6.6 The overt state also included hospital admissions due to hepatic encephalopathy episodes. In the RFHE3001 trial, 19 of the 31 patients (61.29%) in the rifaximin-α group and 36 of the 73 patients (49.32%) in the placebo group who experienced an overt breakthrough episode were hospitalised based on these overt episodes. The 6-month probability (61.29% and 49.32%) was converted to monthly probabilities of 14.63% and 10.71% respectively (assuming a constant hazard over time) and applied to the patients predicted to reach the overt health state.

6.7 The utility values used in the model were derived from 200 randomly selected members of the general public across Greater London, UK using the time-trade-off and standard gamble approach. This was commissioned by the manufacturer because no appropriate generic preference based measure of quality of life was used in the RFHE3001 trial and the data identified from the literature search was not considered by the manufacturer to be appropriate for this analysis. Utility values ranging from 0 for death to 1 for full health were obtained for the 5 health states valued (Conn scores 0,1,2,3 and 4). Multiple regression analyses was then used to assess the relationship between the baseline variables (such as age, sex, income, preference value for their current health) associated with the preference values for each health state. The utility values used in the model (remission [redacted], overt [redacted], death 0) were based on the mean utilities for each Conn score weighted by the proportion of patients in each Conn score category in the overt and remission states. The utility values applied in the model were adjusted to incorporate the effect of aging in the base-case analysis. The values estimated with the time-trade-off approach were used in the base case while those from the standard gamble approach were used in sensitivity analyses. A sensitivity analysis was also conducted where the age adjustment was removed.

6.8 The average monthly cost of rifaximin-α (£281.80) used in the model was based on the recommended dosing schedule of 550 mg twice daily at a unit price of £259.23 per 56-tablet pack. Average monthly lactulose costs (£6.64 and £7.31) for the rifaximin-α and placebo groups respectively were obtained from BNF 64 based on the mean dose of concomitant lactulose in the RFHE3001 trial (3.14 cups for the rifaximin-α group and 3.51 cups for the placebo group). No administration cost was included in the model because rifaximin-α and lactulose are taken orally, therefore the total costs of treatment per month was £288.34 for the rifaximin-α group compared with £7.31 for the placebo group.

Table 1 Unit costs associated with the therapies in the economic model

Treatment	Avg. daily dose	Unit size	Unit price	Cost per day	Cost per month	Total cost (per month)	Reference
Rifaximin (mg)	1100	550	£4.63	£9.26	£281.80	**£288.34**	MIMS
Lactulose concomitantly used with rifaximin (mL)	47.1	500	£2.28	£0.21	£6.64		BNF
Lactulose concomitantly used with placebo (mL)	52.65	500	NA	£0.24	£7.31	**£7.31**	BNF

Source: manufacturer's submission (table 42, page 121)

6.9 A cost of £110.68 for an outpatient visit for a patient in remission was based on NHS reference cost for 2011/2012 and the frequency of the visits of every 3-6 months was based on expert opinion. Based on the manufacturer's assumption of 3-monthly outpatient visits, the monthly cost of an outpatient visit in the remission state was estimated to be £36.89. It was assumed in the model that all patients with overt hepatic encephalopathy incurred the cost of an outpatient visit (£110.68). The hospital admission costs used in the model were estimated using the NHS reference cost for 2011/2012 and was based on the monthly average from the RFHE3001 trial (14.63% and 10.71%, rifaximin-α and placebo) and a mean length of stay of 5 days. This resulted in a total monthly cost

(outpatient visit plus hospital admission) of £359.73 and £292.96 for the overt state for the rifaximin-α and placebo groups respectively. No costs were included in the model for adverse events because the RFHE3001trial did not show any statistically significant differences between the rifaximin-α group and placebo group and there was limited evidence available for disutilities associated with the adverse events. This approach was validated by manufacturer's clinical experts.

Table 2 List of health states and associated costs in the economic model

Health states	Items	Value	
		Rifaximin	**Placebo**
Remission	Technology	£288.34	£7.31
	Outpatient attendance	£36.89	£36.89
Overt	Technology	£288.34	£7.31
	Inpatient hospital stay	£249.05	£182.28
	Outpatient attendance	£110.68	£110.68

Source: manufacturer's submission (table 48, page 123)

6.10 The base case results of the economic analysis showed an incremental cost of £4347.50 and an incremental QALY gain of 0.1875 for rifaximin-α plus concomitant lactulose compared with placebo plus concomitant lactulose. This resulted in an incremental cost effectiveness ratio (ICER) of £23,186 per QALY gained.

Table 3 Base case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Placebo	820.71	1.0304	-	-	
Rifaximin	5168.21	1.2179	4347.50	0.1875	£23,186
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Source: manufacturer's clarification response (page 20)

6.11 The manufacturer also compared the number of first overt breakthrough hepatic encephalopathy episodes and number of deaths estimated from the model at 6 months with those observed in the RFHE3001 trial. The

number of first breakthrough episodes in the model was lower (rifaximin-α: 21; placebo: 56) than those in the clinical trial (rifaximin-α: 31; placebo: 73). The manufacturer explained that this was because of the increased number of deaths in the model (rifaximin-α: 68; placebo: 81) compared with the clinical trial (rifaximin-α: 10; placebo: 11) because of which more patients die before they experience a first breakthrough episode. This was a result of the additional mortality risks applied in the model using external data sources to reflect the range of patients who would present with hepatic encephalopathy in clinical practice.

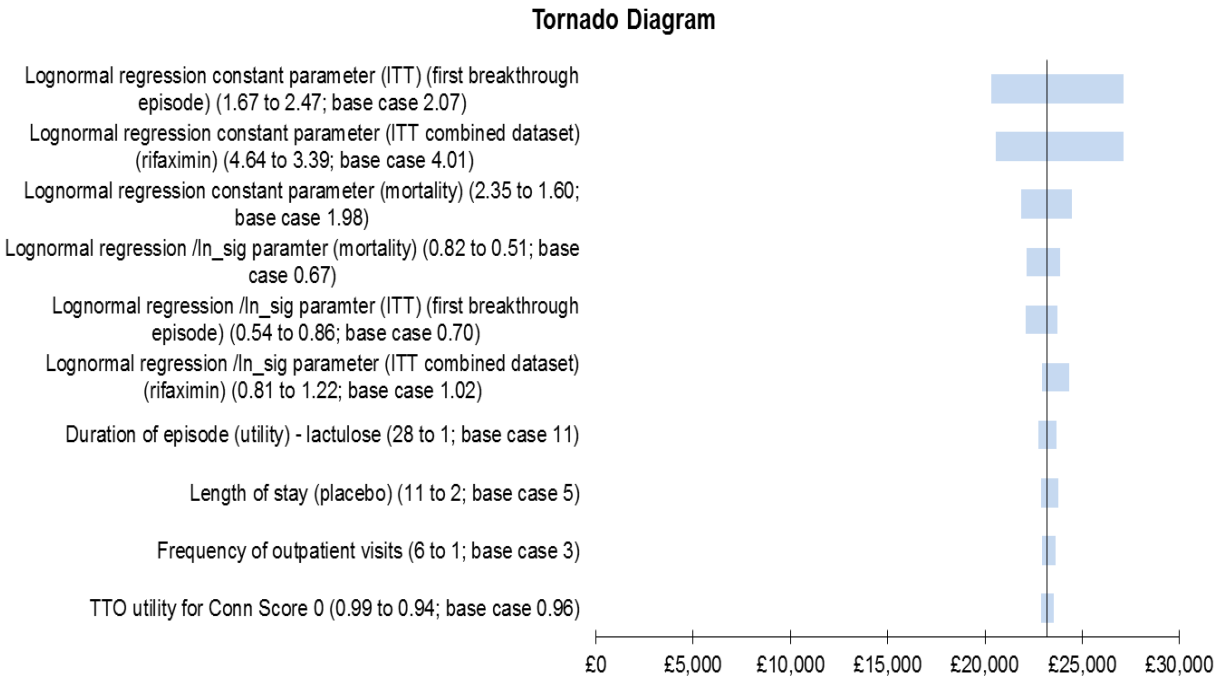
Table 4 Model results compared with RFHE3001 trial outcomes

Outcome	Treatment	Clinical trial result (6 months - RFHE3001)	Model result (6 months)
Number of first breakthrough episodes of HE in RFHE3001	Rifaximin	31	21
	Placebo	73	56
Deaths observed at 6 months	Rifaximin	10	68
	Placebo	11	81

Source: manufacturer's submission (table 49, page 125)

6.12 The manufacturer performed a 1-way deterministic sensitivity on several model parameters using their 95% confidence intervals. The cost-effectiveness result was most sensitive to changes in the parameters used in the extrapolation of time to first breakthrough hepatic encephalopathy episode from the RFHE3001 trial, with ICERs ranging from £20,345 to £27,121 per QALY gained. Changes in hospital length of stay and percentage hospitalised, frequency and cost of outpatient visits and time-trade-off utility for the Conn scores, average daily dose of lactulose, non-malignant liver disorders and liver failure disorders with and without interventions had limited impact on the ICER with results ranging from £22,858 to £23,785 per QALY gained.

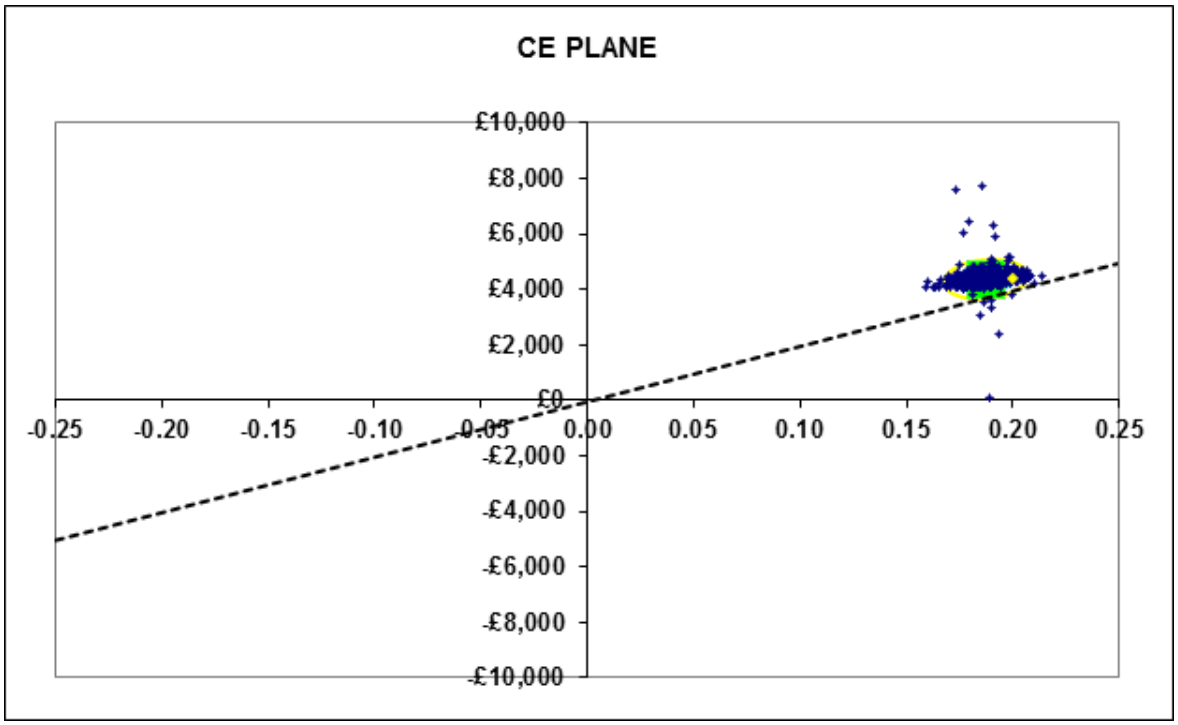
Figure 3 Tornado diagram – univariate deterministic sensitivity analysis



Source: manufacturer's submission (figure 21, page 129)

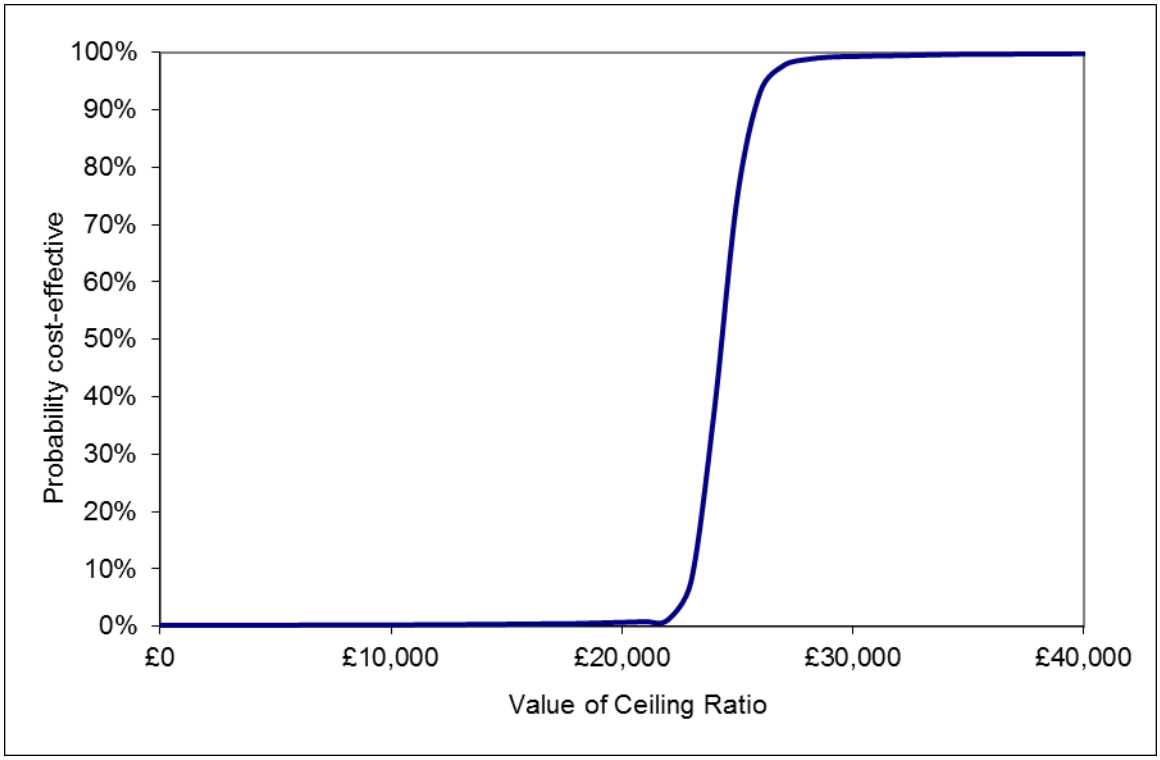
6.13 The manufacturer's probabilistic sensitivity analysis indicated that rifaximin-α plus concomitant lactulose would have a 1.6% and 99.6% chance of being cost-effective compared with lactulose alone, if the maximum acceptable ICER was £20,000 and £30,000 per QALY gained respectively. The ICER estimated from the mean incremental costs and mean incremental QALYs was £23,373 per QALY gained (95% CI £21,500 to £26,048 per QALY gained).

Figure 4 Cost effectiveness plane



Source: manufacturer's submission (figure 22, page 131)

Figure 5 Cost effectiveness acceptability curve



Source: manuacturer's submission (figure 23, page 133)

6.14 The manufacturer also explored various scenario analyses to account for the uncertainties associated with some of the assumptions in the base case model. Alternative parametric distributions based on proportional hazards metric (exponential, Gompertz and Weibull) were used to extrapolate survival and this resulted in ICERs of £15,032, £14,311 and £28,844 per QALY gained respectively. In response to clarification, the manufacturer also presented results using the Gamma and log-logistics distributions which were £25,752 and £23,186 per QALY gained respectively. In another scenario, the manufacturer excluded all-cause mortality from the model to account for the fact that this may have already been included in estimates of the disease specific mortality obtained from the external sources. However, this did not result in any significant change with an ICER of £23,012 per QALY gained.

6.15 Excluding age-adjustments for utility values and using alternative data sources for estimating utility values (standard gamble approach and the study by Wong et al. 1998) also did not lead to significant changes with ICERs of £23,186, £24,439 and £26,431 per QALY gained respectively. The manufacturer also tested the assumption that the severity of episodes in the overt state were evenly spread across Conn scores 1 to 4 (that is, 25% of patients in each Conn score) rather than the proportions from the RFHE3001 trial used in the base case model. As a result, the ICER decreased to £17,155 per QALY gained. When treatment compliance was based on the observations in the RFHE3001 trial (84.3% rifaximin-α and 84.9% placebo) rather than 100% compliance assumed in the base case model, the ICER was also reduced to £19,599 per QALY gained. The manufacturer highlighted that the cost-effectiveness result was primarily driven by the parameters used to extrapolate the time to first breakthrough episode from the trial due to differences between the curves, that is, the magnitude of the treatment effect.

6.16 The manufacturer carried out 2 subgroup analyses based on lactulose use in the RFHE3001 trial. Subgroup A included patients in the rifaximin-α

and placebo groups who had concomitant lactulose (91.3%) and subgroup B was made up of the patients who did not receive concomitant lactulose in the trial (8.7%). The manufacturer advised that subgroup B should be viewed with particular caution because of the small number of patients (rifaximin-α, n=12 and placebo, n=14) which may result in spurious differences in the treatment effect between the two groups. Both analyses resulted in higher ICERs of £25,785 per QALY gained for subgroup A for rifaximin-α in combination with lactulose compared with placebo plus lactulose and £36,254 per QALY gained for subgroup B for rifaximin-α alone compared with placebo alone.

Evidence Review Group comments

6.17 The ERG was satisfied with the manufacturer's modelling approach and agreed that the health states in the model appropriately captured disease progression over time. Clinical opinion obtained by the ERG confirmed that the manufacturer's assumption of concomitant lactulose use in both arms of the model was appropriate, but emphasised that the effectiveness results were based on 91.3% of patients using rifaximin-α with concomitant lactulose and only 8.7% taking rifaximin-α alone.

6.18 The ERG stated that a 5 year time horizon was appropriate to capture the relevant costs and benefits. The ERG noted that approximately 10% of patients remained alive at the end of the 5-year period in the model. However, clinical expert opinion indicated that the surviving patients were likely to be people with stable liver disease. It agreed that a half-cycle correction was not required in the model. The ERG noted that the manufacturer used 2 different cycle lengths in its model (28 days in some cases, such as utility calculations and 30.4 in others). For consistency, the ERG updated the model to reflect a cycle length of 30.4 days in all cases and noted that the impact on the ICER was a minimal increase to £23,613 per QALY gained. The ERG also identified some inconsistencies with the number of patients experiencing a hepatic encephalopathy episode, the percentages of patients in the Conn score categories which were used to

calculate utility values, and also noted that mortality rates did not add up to 100%. The impact of these inconsistencies was explored in a scenario analysis where the percentage weights attached to the Conn score categories were recalculated, so that the total population adds up to 100%. This recalculation reduced the ICER to £21,929 per QALY gained.

6.19 The ERG noted that the manufacturer's choice of the log-normal distribution was based only on the assessment of best model fit using the AIC, BIC and visual inspection whereas several other steps should also have been undertaken. For example, the ERG stated that internal validity of the choice should have been assessed using log-cumulative hazard plots (which the manufacturer provided during clarification) as well as quantile-quantile plots to assess the suitability of the proportional hazards and acceleration factor (time ratio) assumptions. The ERG also stated that the expected hazard over time should have been compared with that predicted by the parametric models or using expert opinion to ensure external validity. In addition, though sensitivity analysis using alternative models was presented, the models chosen were not appropriately justified. The ERG highlighted that when other distributions were used to fit the data, the final ICER varied significantly in some cases ranging from £21,850 per QALY gained with a log-logistic distribution to £28,844 per QALY gained using a Weibull distribution.

6.20 The ERG noted that the manufacturer used the combined dataset from the RFHE3001 and RFHE3002 studies in the rifaximin-α arm data from the RFHE3002 study was used for the placebo arm. The ERG stated that this approach was reasonable as it allowed all available data to be incorporated and there was no risk of bias because the population in the RFHE3002 follow-up study were patients continuing rifaximin-α from the RFHE3001 trial. However, the ERG stated that the manufacturer took the shape parameter from the regression run to fit the data for the rifaximin-α arm and used it to replace the shape parameter estimated from the log-normal distribution fitted to the placebo arm. The ERG expressed concern

that this could potentially lead to the incorrect estimation of the effectiveness in the treatment arm, and that this was supported by the sensitivity analysis conducted by the manufacturer which indicated that varying the values of the shape parameters had a considerable impact on the ICER.

6.21 The ERG stated, based on clinical expert opinion, that the manufacturer's assumption of a constant probability of subsequent episodes over time was not reflective of reality. It was also concerned that the use of an exponential distribution, which implies a constant and proportional hazard between treatment arms, did not appear to be a good fit to data based on AIC, BIC and visual inspection. The ERG also examined the data from the RFHE3002 study for patients who experienced 1 or more hepatic encephalopathy episodes over 2 years.

[redacted] The ERG stated that the impact of this assumption was not easily foreseen and highlighted that this may be a potential driver of uncertainty in the ICER estimated. The ERG considered the manufacturer's use of external data to model hepatic encephalopathy-specific mortality to be appropriate because it captured mortality rates for a wider group of people with hepatic encephalopathy. It noted that the mortality assumed for Conn score categories 3 and 4 may have been overestimated and when these were changed to lower values, the overall mortality in the overt state would decrease resulting in a higher ICER. It also highlighted that the difference in mortality rates in the overt and remission states was a key driver of the difference in QALYs across treatment groups.

6.22 The ERG was satisfied with the calculation of costs in the model, although it considered that the estimation of lactulose cost should have been based on the proportion of patients who received lactulose in the RFHE3001 trial. It re-calculated the cost of lactulose based on lactulose use in the

RFHE3001 trial in a scenario analysis, but the ICER remained almost the same as the base case (£23,185 compared with £23,186 per QALY gained in the base case). When this correction was considered together with the other adjustments in the model (see section 6.18), the ICER reduced to £22, 298 per QALY gained. The ERG noted that the manufacturer did not include costs for adverse events because they were comparable between the rifaximin-α and placebo groups in the pivotal trial, but stated that the inclusion of relative risks (or risk difference) and 95% confidence intervals for each adverse event would have strengthened this justification. However, the ERG also stated that the inclusion of adverse events in the costs and QALY calculations would not have a significant impact on the ICER based on the nature of the drug-related adverse events [redacted] and the proportion of patients that experienced them in the RFHE3002 trial ([redacted]).

6.23 The ERG noted that the manufacturer's subgroup analysis on the concomitant use of lactulose was not based on pre-planned subgroup analysis in the RFHE3001 trial. Nevertheless, it considered the analysis to be informative to some extent, but advised that the results should be interpreted with caution, especially due to small sample size in subgroup B (those that did not receive lactulose, 8.7% of the RFHE3001 trial population). The ERG also stated that the 1-way sensitivity analysis had not been clearly presented and was concerned that some parameters were excluded, such as the exponential regression parameters used to model subsequent episodes and the log-normal constant parameter used to model time to first hepatic encephalopathy episode in the placebo arm. It performed a 1-way sensitivity analysis for these parameters and the resulting ICERs ranged from £20,345 to £26,105 per QALY gained. The ERG also identified a linking mistake in the model which had an impact on the probabilistic parameters in the log-normal distribution used to model time to first breakthrough episode in the rifaximin-α arm. Correcting this mistake suggested that the ICER estimated from the probabilistic

sensitivity analysis may vary across a wider range than the one reported by the manufacturer (values not reported).

6.24 The ERG was also concerned about the justification of the alternative distributions explored in the manufacturer's scenario analyses. The manufacturer stated in response to clarification that this intended to explore results based on the proportional hazards metric (see section 6.14), but the ERG expressed concerns given that different assumptions guide the acceleration failure time (AFT) models and the proportional hazards models. The ERG explained that AFT models such as the log-logistics or log-normal models (in some cases Weibull model) assess how fast a specific outcome occurs in the treatment arm compared with the control arm (that is, time ratio across treatments), while the proportional hazards models such as the exponential, Gompertz and in some cases the Weibull models assess the relationship between the proportion of events in both treatment arms. Based on this the ERG indicated that the log-logistic model was the most appropriate model to compare with the log normal model in a scenario analysis and estimated that using the log-logistic distribution would result in an ICER of £21,850 per QALY gained.

6.25 The ERG noted the manufacturer's justification for excluding neomycin as a comparator (see section 6.1) but remained concerned about its exclusion because clinical expert opinion indicated that it works through the same process as rifaximin-α and it is sometimes used in clinical practice especially in people that will not undergo liver transplantation, even though it is not as well tolerated as rifaximin-α. Although the ERG acknowledged the manufacturer's justification for excluding the study by Miglio et al., it presented a scenario analysis for illustrative purposes using data from the study. Based on the assumption of equal effectiveness as demonstrated in the study, the ERG replaced the cost of rifaximin-α with the cost of neomycin in the model. The daily cost of neomycin was estimated as £1.63 based on the recommended dose of 4 g daily (for hepatic coma) at a unit price of £20.36 for a 500 mg, 100-tablet pack

taken from the BNF. The treatment was assumed to last 6 days per month. Given that neomycin is considerably cheaper than rifaximin-α, the ICER reduced to £692.48 per QALY gained for neomycin plus lactulose compared with lactulose alone. Based on this, the ERG stated that neomycin represents a more cost-effective alternative than rifaximin-α for the patients that respond to neomycin.

7 Equalities issues

7.1 No potential equality issues were identified at the scoping stage or in the evidence submitted.

8 Innovation

8.1 The manufacturer stated that there was an unmet need for effective treatments to manage people with liver cirrhosis who experience hepatic encephalopathy. It stated that rifaximin-α was expected to offer a step-change in the management of hepatic encephalopathy given that it has been shown to significantly reduce breakthrough hepatic encephalopathy episodes and hospitalisations as well as improve health-related quality of life significantly compared with placebo as shown in the RFHE3001 trial (noting that 91% of patients in the trial received lactulose). The manufacturer stated that there were potential health-related benefits that were unlikely to be included in the QALY calculation given the variable length and nature of episodes of hepatic encephalopathy which makes capturing of quality of life difficult in these people. The manufacturer also indicated that reducing the recurrence of hepatic encephalopathy symptoms would likely have an impact on the health and quality of life of carers as shown in the study by Bajaj et al. 2011, which showed that there was a direct correlation between key cognitive tests and burden on caregivers.

9 Authors

Nwamaka Umeweni

Technical Lead

Raisa Sidhu

Technical Adviser

with input from the Lead Team (Dr John Radford, Professor Steven Julious and Paddy Storrie)

Appendix A: Supporting evidence

Related NICE guidance

There is no related guidance for this technology.

Appendix B: Clinical efficacy section of the draft European public assessment report

Rifaximin completed the decentralised assessment procedure, with the UK as Reference Member state. The public assessment report is available from:

http://www.mhra.gov.uk/Publications/PublicAssessmentReports/A-Zlisting/index.htm?indexChar=T