Rifaximin for preventing episodes of overt hepatic encephalopathy

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1   Rifaximin is recommended, within its marketing authorisation, as an option for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older.

2 The technology

2.1   Rifaximin (Targaxan, Norgine) is a semi-synthetic derivative of the antibiotic rifamycin. 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. Rifaximin has a marketing authorisation in the UK '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 people in the pivotal study were using concomitant lactulose.

2.2   The summary of product characteristics lists the following common adverse reactions for rifaximin: depression, dizziness, headache, dyspnoea (shortness of breath), upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites (accumulation of fluid in the abdominal cavity), rashes, pruritus (itching), muscle spasms, arthralgia (joint pain), and peripheral oedema (swelling). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3   Rifaximin is available as 550 mg film-coated tablets at a net price of £259.23 per 56-tablet pack (excluding VAT; BNF online [accessed December 2014]). It is administered orally at a recommended dose of 550 mg twice daily. The company estimated an average cost of £1,689.65 for 6 months of treatment. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee considered evidence submitted by the company (Norgine) that holds the UK marketing authorisation for rifaximin and reviews of these submissions by the Evidence Review Groups (ERGs). The company provided 4 submissions, referred to in this document as the 'original', 'October 2013', 'December 2013' and 'November 2014' submissions; each was reviewed by an ERG.

Clinical-effectiveness evidence

3.1 The company conducted a systematic literature review and identified 3 relevant published studies including rifaximin. Of these, 2 studies were excluded because the doses used were different from those in the UK marketing authorisation for rifaximin. The submission therefore included 1 published study (Bass et al. 2010), which reported results from the pivotal trial, RFHE3001. This was a 6 month, international, multicentre, randomised, double-blind trial comparing rifaximin with placebo for maintaining remission in people with recurrent, overt, episodic hepatic encephalopathy resulting from chronic liver disease. People taking lactulose at baseline were allowed to continue its use during the study period and dose changes were allowed as needed. The company also identified a second trial, RFHE3002; this was an international, multicentre, single-arm, open-label study that assessed the long-term safety and tolerability of rifaximin in people with a history of hepatic encephalopathy. It was an extension to RFHE3001 for people who completed RFHE3001, and for newly enrolled people.

RFHE3001 trial

3.2 People were enrolled in RFHE3001 if they had a Conn score of 0 or 1 and were in remission after documented recurrent episodes of overt hepatic encephalopathy (2 or more episodes, equivalent to a Conn score of 2 or more, in the 6 months before screening) associated with chronic liver disease or portal hypertension. The Conn score measures the severity of impaired mental status on a scale of 0 to 4, with higher scores indicating more severe impairment. Baseline characteristics were generally similar between the 2 treatment groups. People

were only enrolled if they had a Model End Stage Liver Disease score (MELD; used to predict survival to prioritise liver transplant) of less than 25. Therefore, people with more severe liver disease (MELD score of 25 or more) were excluded from the study. After screening, 299 people were randomised to have either rifaximin 550 mg (rifaximin group; n=140) or matching placebo (placebo group; n=159) twice daily, plus ongoing treatment with lactulose. In the rifaximin and placebo groups, 91.4% and 91.2% of people took concomitant lactulose, respectively. The mean duration of treatment was 130.3 days in the rifaximin group and 105.7 days in the placebo group. The rate of adherence, defined as the use of at least 80% of dispensed tablets, was high in both treatment groups (84.3% in the rifaximin group and 84.9% in the placebo group). People could stop treatment if they had an adverse event with an unacceptable risk to them, developed any condition meeting the exclusion criteria, had a breakthrough episode of overt hepatic encephalopathy, became pregnant or asked to be withdrawn.

3.3   The primary outcome in RFHE3001 was time to first breakthrough episode of overt hepatic encephalopathy. An episode of overt hepatic encephalopathy was 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 people who entered the study with a Conn score of 0. The asterixis score measures worsening neurological impairment in terms of flapping tremor, which is determined by the person 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 admission

- time to any increase from baseline in Conn score

- time to any increase from baseline in asterixis score

- 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 to measure people's level of fatigue on a 7-point scale,

with '1' representing a high degree of fatigue and '7' representing minimal fatigue. All results were based on the intention-to-treat (ITT) population, that is, everyone who was randomised and had at least 1 dose of the study drug or placebo. In addition to the CLDQ, health-related quality of life was assessed using the SF-36 and the Epworth Sleepiness Scale.

3.4   There was a statistically significant reduction in the risk of a breakthrough episode with rifaximin 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. People who stopped early for reasons other than a breakthrough episode of overt hepatic encephalopathy were contacted 6 months after randomisation to check if they had a breakthrough episode. The company stated that breakthrough episodes of overt hepatic encephalopathy were therefore captured completely for up to 6 months after randomisation. People who did not have a breakthrough episode during the study period were followed up and assessed after the study was stopped. Their results were similar to the results for the 6-month study period, with a statistically significant reduction in the risk of a breakthrough episode with rifaximin compared with placebo (HR 0.46; 95% CI 0.31 to 0.69, p<0.0001).

3.5   Age, MELD score, duration of current verified remission and number of prior hepatic encephalopathy episodes were identified as important prognostic factors. To control for these factors because of chance imbalances between treatment groups, multivariate analysis was done using the Cox proportional hazards model. This resulted in a statistically significant reduction in the risk of a breakthrough episode of overt hepatic encephalopathy with rifaximin compared with placebo (HR 0.40; 95% CI 0.26 to 0.62, p<0.0001).

3.6   Analyses of secondary outcomes showed that rifaximin was associated with statistically significant reductions compared with placebo in the risk of first hepatic encephalopathy-related hospital admission (HR 0.50; 95% CI 0.29 to 0.87, p=0.01) and the risk of any increase from baseline in Conn score (HR 0.46; 95% CI 0.31 to 0.69, p<0.0001). However, the reduction in risk of any increase from baseline in asterixis score with rifaximin did not reach statistical significance when compared with placebo (HR 0.65; 95% CI 0.41 to 1.01, p=0.0523). The differences in the changes from baseline in CLDQ 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 and placebo groups respectively). The company stated that this was because people were not able to complete the CLDQ assessment during a breakthrough episode because of altered mental and neuromotor status. Therefore, the CLDQ results at the end of treatment for people who had a breakthrough episode would be similar to their baseline results, because their mental status would be expected to return to close to baseline levels at the end of treatment (that is, after the episode had resolved). The company also stated that there were no consistent differences between the rifaximin and placebo groups in change from baseline using the SF-36 and Epworth Sleepiness Scale. The rifaximin group had greater reductions in venous ammonia levels compared with the placebo group, although the difference was not statistically significant (p=0.0818). The company stated that the mortality data from the trial were not mature enough to address the impact of rifaximin on survival.

3.7   Pre-planned subgroup analyses of a subgroup with MELD scores of 19 to 24 (26 of the 299 people) and a subgroup of those who were not taking lactulose at baseline (26 of the 299 people) were carried out. The analyses showed that the effect of rifaximin in reducing the risk of breakthrough episodes of overt hepatic encephalopathy compared with placebo during the 6-month study period was not statistically significant in these groups (p=0.21 and p=0.33 respectively). The company considered that this was primarily because of small numbers in these groups.

3.8   The safety population (n=299) was described by the company as people who had at least 1 dose of study drug and provided at least 1 post-baseline safety assessment. In the rifaximin group, 80% of people had adverse events during the study compared with 79.9% in the placebo group. Most adverse events were mild or moderate. The rifaximin group had higher incidences of anaemia (rifaximin compared with placebo; 7.9%: 3.8%), peripheral oedema (15%: 8.2%), fever (6.4%: 3.1%), joint pain (6.4%: 2.5%) and dizziness (12.9%: 8.2%) than the placebo group. Treatment-related adverse events occurred in 19.3% of people in the rifaximin group compared with 21.4% in the placebo group. Approximately 11.4% of people in the rifaximin group and 21.4% in the placebo group had breakthrough episodes of overt hepatic encephalopathy that were considered serious adverse events (for example, needing hospital admission). A total of 10 (7.1%) people in the rifaximin group and 11 (6.9%) people in the placebo group died during the study, mainly because of conditions associated with disease progression. These

included hepatic cirrhosis, decompensated liver cirrhosis or hepatic failure. Adverse events leading to study discontinuation occurred in 21.4% of people in the rifaximin group compared with 28.3% of people in the placebo group. The company stated that most of the study discontinuations from adverse events were caused by hepatic encephalopathy events. Adverse events of special interest based on known potential side effects of systemic antibiotics and prior experience with rifaximin occurred similarly between the treatment groups, with diarrhoea being the most common (10.7% with rifaximin and 13.2 % with placebo).

RFHE3002 trial

3.9   A total of 322 people were enrolled in the RFHE3002 single-arm, open-label study. Of these, 152 continued from RFHE3001 (70 people from the rifaximin group and 82 from the placebo group) and 170 people were newly enrolled. All people had a Conn score of 0 to 2 at enrolment and the newly enrolled people had 1 or more verifiable hepatic encephalopathy episodes in the 12 months before screening. All people had rifaximin 550 mg twice daily and were followed up for at least 24 months. During this time treatment was still ongoing on an outpatient basis until regulatory approval of rifaximin or until the company closed the study, whichever came first. All concomitant drugs, including those from RFHE3001, were maintained at stable doses whenever possible. The criteria for study discontinuation were the same as those for RFHE3001, although people who had an episode of recurrent hepatic encephalopathy during the study were not automatically withdrawn and were allowed to continue on medication.

3.10   Most people had baseline Conn scores of either 0 (66%) or 1 (30%) and asterixis scores of 0 (71%) or 1 (24%). The time since the most recent verified hepatic encephalopathy episode was shorter in the newly enrolled group than in the continuing group. The 2 groups of people were also different in terms of the number of hepatic encephalopathy episodes they had before screening for RFHE3002 because of the differences in the number of hepatic encephalopathy episodes needed for inclusion in the 2 studies. The company indicated that the rest of the baseline characteristics were commercial-in-confidence, and therefore they cannot be reported here.

3.11   The main efficacy outcomes assessed were change from baseline in Conn scores

and asterixis scores over time. However, the company indicated that these results were commercial-in-confidence, and therefore they cannot be reported here. The company stated that the profiles of the time to first breakthrough episode of overt hepatic encephalopathy demonstrated long-term maintenance of remission in the newly enrolled group and the continuing group. In addition, 60 people treated with rifaximin in RFHE3001 who had not had an episode of hepatic encephalopathy were followed during RFHE3002. The incidence of breakthrough episodes for these people was lower than in the RFHE3001 placebo group, after adjusting for the different exposure time between rifaximin and placebo. The company also stated that the all-cause hospital admission rate was similar to that seen for rifaximin during the shorter double-blind trial. However, hazard ratios were not presented.

3.12   A total of 300 people (93.2%) reported an adverse event in RFHE3002 and approximately 56% of people taking rifaximin had severe adverse events. Overall, 67 deaths occurred during the study or within 30 days after the last dose of rifaximin and 8 people died more than 30 days after their last dose. The company stated that none of these deaths were related to rifaximin. The company indicated that the treatment-related adverse events, severe adverse events and adverse events that resulted in people stopping the study were commercial-in-confidence, and therefore they cannot be reported here.

Other studies

3.13   The company presented evidence, in the November 2014 submission, from audits of rifaximin use in clinical practice at 4 centres in the UK (Dundee, Bristol, Newcastle and Bolton) and carried out a meta-analysis of the data. The company noted that other audits had been carried out but were not included in the meta-analysis. These were an audit carried out in Portsmouth and a multicentre audit to be published by Orr et al. in 2015, which were not available in time for the analysis (although an abstract of Orr et al. was provided with the submission), and a multicentre audit published by Patel et al. (2014), which the company considered to be too heterogeneous and too short in duration. The audits compared the number of hospital admissions and the duration of these admissions, before and after starting treatment with rifaximin ('without rifaximin' and 'with rifaximin' respectively). The audits showed that treatment with rifaximin

was associated with statistically significant decreases in the number of hospital admissions and the number of bed days, compared with treatment without rifaximin. The meta-analysis showed a pooled estimate of 1.25 fewer hospital admissions per patient per year (95% CI 0.66 to 1.83, p<0.001), and 22.18 fewer bed days per year (95% CI 9.10 to 35.27, p<0.001) with rifaximin treatment, compared with treatment without rifaximin. The results of the Bolton audit were different to the other 3 audits, and when Bolton was excluded, the heterogeneity of the analysis of bed days decreased and the pooled estimate changed to 16.543 fewer bed days (95% CI 9.084 to 24.003, p<0.001) with rifaximin treatment. The company also presented Hospital Episode Statistics on hospital stays for hepatology-related disorders between 2010 and 2013 (the same period as the audits). It noted that there was no meaningful reduction in overall bed stays during this period. The company considered that this showed that the reductions in bed stays seen in the audits were related to rifaximin, and not to broader efficiency programmes within the NHS at that time.

3.14 In the November 2014 submission, the company highlighted additional evidence that supported the long-term efficacy of rifaximin and the effect of rifaximin on mortality. It noted 2 studies that provided efficacy data with up to 5 years' follow-up, and 3 further studies from international centres that had follow-up periods greater than 6 months. The company also highlighted 3 studies that showed statistically significant improvements in survival in people treated with rifaximin, compared with the respective control groups, and a meta-analysis that found that rifaximin treatment was associated with reduced mortality.

Cost-effectiveness evidence

3.15 The company carried out a systematic literature review but stated that of the 3 studies identified, none were relevant because the population and outcomes did not match those of the current decision problem. The company stated that a comparison with neomycin was excluded because it is not routinely used in clinical practice, no clinical data are 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.

3.16 The company carried out a de novo analysis of the cost effectiveness of rifaximin

plus concomitant lactulose compared with placebo plus concomitant lactulose, given that approximately 91% of people in each arm of RFHE3001 had concomitant lactulose. The 2 arms of the model are referred to in this document as the 'rifaximin' and 'lactulose' arms respectively. The company presented 4 iterations of its economic model, with its 4 submissions (referred to in this document as 'original', 'October 2013', 'December 2013' and 'November 2014'). The October 2013 submission was prepared after the first consultation, and incorporated updates to the clinical-effectiveness inputs, mortality estimates, hospital admission rates and utility estimates. The December 2013 submission explored additional issues raised by the Committee in the second appraisal consultation document, relating to estimates of utility, the mortality benefit associated with rifaximin and the time horizon. The November 2014 submission provided further exploration of utility scores and incorporated evidence from clinical audits to inform the rate and duration of hospital admissions.

3.17   In the original submission, the company developed a Markov cohort model consisting of 5 states to reflect the clinical pathway of hepatic encephalopathy. The health states are referred to in this document as initial remission, breakthrough overt episode, subsequent remissions, subsequent overt episodes and death. The company noted (November 2014) that the remission states could also be described as covert hepatic encephalopathy, because the symptoms of hepatic encephalopathy do not completely resolve. Given that time to subsequent episodes was not available from RFHE3001, the company assumed that the risk of having a subsequent breakthrough episode was independent of the risk of preceding episodes and the time spent in the remission state. It was 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. However, in response to the Committee's considerations in the first appraisal consultation document, that the assumptions in the original model oversimplified the nature and course of the disease, the company submitted the October 2013 analysis in which the risks of subsequent episodes were based on data on time to subsequent events from RFHE3002. The original and October 2013 models had a time horizon of 5 years; the December 2013 and November 2014 analyses used a lifetime (42-year) time horizon. The models used monthly cycles, did not include a half-cycle correction, and included both costs and benefits discounted at 3.5%. The analyses were done from the perspective of the NHS and personal social

services.

3.18   In the original submission, time to first breakthrough episode of hepatic encephalopathy was extracted and combined from the Kaplan–Meier survival curves in RFHE3001 and RFHE3002. The combined data set was extrapolated, using the log normal distribution, to estimate the effectiveness of rifaximin beyond the final 168-day observation point in RFHE3001. However, in its October 2013 analysis the company took into account the Committee's comments that the use of a combined data set was not appropriate. It used data from RFHE3001 only to model time to first breakthrough episode of hepatic encephalopathy for the rifaximin and lactulose arms, and survival times were censored at day 170. The survival curves were then extrapolated beyond 170 days for both groups using a log normal distribution and a proportional hazards assumption. To model subsequent hepatic encephalopathy episodes (for which there were no data from RFHE3001), the company used data from only the newly enrolled people in RFHE3002 to avoid potential bias from people who had been in RFHE3001 and did not have a breakthrough overt episode in RFHE3001. Because RFHE3002 was a single-arm study (rifaximin only), the company applied the rifaximin treatment effect from RFHE3001 to the RFHE3002 data for all subsequent events. All subsequent episodes were modelled together as a single health state. As for the first overt episode, the survival curves for subsequent overt episodes were extrapolated to 5 years using the log normal distribution and applying an assumption of proportional hazards. The company considered the log normal distribution to provide the best model fit in both cases based on the log likelihood values of the distributions tested and visual assessment.

3.19   The company also presented 3 separate analyses to justify using RFHE3002 data in the economic model. The analyses included:

- comparing time to first observed breakthrough hepatic encephalopathy episode between the RFHE3002 subgroups, that is, rollover (people previously enrolled in RFHE3001 and treated with rifaximin), crossover (people previously enrolled in RFHE3001 and treated with placebo) and newly enrolled people, from RFHE3002 baseline

- comparing time to first observed breakthrough hepatic encephalopathy episode between RFHE3001 treatment groups and RFHE3002 subgroups, from each respective study baseline

- comparing time to first breakthrough episode between newly enrolled people and the combined RFHE3001 and RFHE3002 data for rollover and crossover people.

  The results of these analyses showed that time to first breakthrough hepatic encephalopathy episode was comparable between people in RFHE3001 and RFHE3002 given the similarity in their baseline characteristics, except in the number of prior hepatic encephalopathy episodes before trial entry (see sections 3.2 and 3.10).

3.20   The company incorporated mortality into the economic model through the modelling of transition into the 'death' health state. In the original submission, hepatic encephalopathy-specific mortality was estimated from other external data sources (Bustamante et al. 1999 and Shawcross et al. 2011) rather than RFHE3001. The company stated that this was because the trial did not provide evidence on people at the more severe end of the disease spectrum, even though it reflected the range of people who would present with hepatic encephalopathy in clinical practice, and that data from the trial were not sufficiently mature for an analysis of mortality. However, the company explored alternative mortality estimates in its October 2013 and December 2013 analyses.

3.21   In the October 2013 economic analysis, the company modelled mortality using data for all people in RFHE3002, and noted the small number of deaths seen. Time to death for the initial remission state was estimated from the first dose of rifaximin in RFHE3002, whereas for the subsequent remission state it was estimated from day 31 after each overt episode (assumed to be when people returned to the remission state after an overt episode). The survival curves were then extrapolated based on an assumption of proportional hazards using the log normal distribution for the first remission state and the Weibull distribution for subsequent remissions taking into consideration the log likelihood and visual assessment of the best model fit. The probability of death for the overt states was estimated as the number of deaths within 30 days of the onset of the first observed overt episode in RFHE3002 and the number of deaths within 30 days of the onset of any subsequent overt episode.

3.22   As part of the October 2013 analysis, the company also carried out a literature review of mortality in people with hepatic encephalopathy and an analysis of the

mortality data for people with hepatic encephalopathy using the Clinical Practice Research Datalink (CPRD). The literature review and CPRD data showed that mortality was highest in the first 6 months after diagnosis of hepatic encephalopathy, which could be associated with the first overt hepatic encephalopathy episode. A study by Neff et al. (2012) showed that people who had lactulose alone had a higher 6-month mortality; 40% compared with 35% for people who had rifaximin plus lactulose and 24% for people who had rifaximin alone. The company also noted from the CPRD data that people who had survived 6 months after the first overt episode had similar mortality to that seen in RFHE3001 and RFHE3002, in which people had been in remission after at least 1 overt episode in the 12 months before randomisation.

3.23   The company noted that in the base case, the risk of death differed between the 4 health states, but that these risks did not differ between the rifaximin and lactulose arms. Consequently, any apparent differences between the groups in mortality resulted from differences in the time spent in each health state (for example, delaying overt episodes), rather than an explicit mortality benefit with rifaximin. Moreover, the company noted that because the time horizon was extended to lifetime (42 years) in the December 2013 analysis, the mortality benefit for rifaximin diminished over time. In its December 2013 analysis, the company presented 3 scenario analyses to explore the impact of the differences in mortality estimates on the results of the economic model:

- In the first scenario, it was assumed that mortality was the same in both of the remission health states.

- In the second scenario, it was assumed that mortality did not increase with overt episodes (compared with the remission health state) and therefore, for each overt episode health state, mortality was the same as for the preceding remission health state.

- In the third scenario, it was assumed that mortality was the same for all 4 health states.

3.24   The overt states also included hospital admissions caused by hepatic encephalopathy episodes. In RFHE3001, 19 of the 140 people in the rifaximin group and 36 of the 159 people in the placebo group were hospitalised; 31 people in the rifaximin group and 73 people in the placebo group had breakthrough

episodes. The company therefore calculated the probability of hospital admission in people who had an episode to be 61.29% and 49.32% in the rifaximin and placebo groups respectively. In the original submission, these 6-month probabilities of hospital admission were converted to monthly probabilities of 14.63% and 10.71% in the rifaximin and lactulose arms respectively (assuming a constant hazard over time) and applied to the people predicted to reach the overt health state. However, in the October 2013 analysis, the company applied the aggregated 6-month probability of 52.88% to both arms of the model. The company used the aggregated 6-month probability rather than individual probabilities of 61.29% for rifaximin and 49.32% for lactulose on the basis that the proportions of overt hepatic encephalopathy episodes that led to hospital admission in the trial were not statistically significantly different between the 2 arms. In the original, October 2013 and December 2013 submissions, the company assumed that each hospital stay lasted 5 days.

3.25   In the November 2014 submission, the company presented analyses incorporating evidence on hospital admission rates and bed stays from audits of clinical practice in the UK (see section 3.13). The company adjusted the model to simulate as closely as possible the number of hospital admissions and bed days seen in these audits. The company assumed that all episodes of overt hepatic encephalopathy led to hospital admission (that is, the probability of admission was set to 100%). It noted that this was necessary because the number of episodes predicted by the model (based on RFHE3001) was lower than seen in clinical practice. The company also adjusted the assumed length of stay for each hospital admission, based on its meta-analysis of the audit data; it presented analyses using the mean reduction in bed days in the meta-analysis of all 4 centres, the mean reduction when Bolton was excluded, and the upper and lower 95% confidence limits for each meta-analysis. In the scenario based on the meta-analysis of all 4 centres, the length of stay was assumed to be 30.6 days in the lactulose arm and 20.2 days in the rifaximin arm.

3.26   The utility values used in the original model were derived from 200 randomly selected members of the general public, using the time-trade-off and standard gamble approach. Noting the Committee's concerns about this approach in the first appraisal consultation document and the Committee's preference for quality-of-life data collected from RFHE3001, the company presented alternative results in the October 2013 analysis. The company used a validated algorithm

developed by Gray et al. (2006) to map the SF-36 utility scores collected in RFHE3001 to EQ-5D utility values. The company also included in the analysis CLDQ scores that were derived from the quality-of-life study by Sanyal et al. (2011). The study reported CLDQ data only for North American and Canadian people from RFHE3001 (219 of 299 people) because there was not a validated Russian translation of CLDQ for Russian people. The company then carried out a regression analysis and a repeated measures analysis to derive and quantify the relationship between overall CLDQ scores from RFHE3001 and EQ-5D utility. The resulting parameter estimate for CLDQ was applied to the baseline CLDQ score, the increment in the CLDQ score for the rifaximin arm while in remission and the CLDQ scores for the overt states, to give utility estimates for the remission and overt health states. The utility estimate for the initial remission health state was used for the lactulose arm in the October 2013 analysis, and a utility increment of 0.106 was applied to this estimate to give the utility associated with remission in the rifaximin arm. Utility values for the overt states were assumed to be the same for the rifaximin and lactulose arms. The utility values used in the model were designated academic-in-confidence by the company, and therefore they cannot be reported here.

3.27   In its December 2013 submission the company provided additional analyses exploring alternative utilities. Although it considered the utility values in its October 2013 analysis to be the preferred approach, in response to a request from the Committee the company presented a scenario analysis in which utility values were obtained by directly mapping the SF-12 subset of SF-36 scores from RFHE3001 to EQ-5D utility values (that is, without the additional CLDQ steps included in the October 2013 analyses described in section 3.26). The company used a mapping method developed by Gray et al. (2006) with multiple imputation to account for missing responses. It presented unadjusted results based on all observations and observations from the remission state only, and it also presented baseline-adjusted results. The company reported that in the unadjusted analysis utility scores for the remission state appeared to increase after baseline, and that people who had an overt episode had lower utility than people in remission. The baseline-adjusted results suggested that utility increased in people treated with rifaximin compared with placebo during the study.

3.28   In its December 2013 analysis, the company presented a scenario in which

people who had rifaximin had a utility increment compared with those in the lactulose arm, based on the utility increment seen in the baseline-adjusted results. For this scenario, the utility scores in the overt states were derived from the study of the general population presented in the company's original model, using the standard gamble methodology. The estimated utility during the remission states for people treated with lactulose was 0.568. Episodes of overt hepatic encephalopathy were associated with a decrease in utility of 0.286 compared with remission. The utility increment associated with rifaximin treatment (compared with lactulose) was 0.032, and this was applied in all 4 health states.

3.29   In its November 2014 analysis, the company stated that clinical opinion suggests rifaximin is associated with an observable improvement in quality of life. The company considered that this shows rifaximin gives an improvement at least as large as the minimum important difference (MID) for utility scores based on EQ-5D. It therefore presented evidence on the MID for EQ-5D. It noted that Walters and Brazier (2005) reported a pooled estimate for the MID for EQ-5D of 0.074 (based on estimates ranging from −0.011 to 0.139) and that Coretti et al. (2014) reported estimates ranging from 0.03 to 0.52. The company presented a scenario analysis in which the utility increment associated with rifaximin in the remission states was equal to the average MID for EQ-5D estimated by Walters and Brazier (that is, 0.074).

3.30   The average monthly cost of rifaximin (£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. In the December 2013 model, average monthly lactulose costs (£8.15 and £9.09) for the rifaximin and lactulose groups respectively were obtained from the BNF 63, based on the mean dose of concomitant lactulose in RFHE3001 (3.14 cups for the rifaximin group and 3.51 cups for the placebo group). No administration costs were included in the model because rifaximin and lactulose are taken orally; therefore, the total drug costs per month in the model were £289.95 for the rifaximin arm compared with £9.09 for the lactulose arm. The company estimated a total monthly cost of £58.76 associated with the remission states, reflecting outpatient visits every 3 months. It estimated costs associated with the overt states using the assumptions that a proportion of episodes led to hospital admission, and that if admitted to hospital people would stay for a given period. In the October 2013

and December 2013 submission, the cost associated with the overt states was £1,040.77, reflecting the assumption that 53% of people were admitted to hospital and stayed for 5 days (see section 3.24); in the November 2014 submission, the cost was adjusted using the revised hospital admission assumptions (see section 3.25). These costs were applied to both the rifaximin and lactulose arms. No costs were included in the model for adverse events because there were no statistically significant differences between the adverse events reported with rifaximin and placebo in RFHE3001 and there was limited evidence available for disutilities associated with the adverse events. This approach was validated by the company's clinical experts.

3.31   The company's original base-case analysis showed that rifaximin was associated with an incremental cost-effectiveness ratio (ICER) of £23,186 per quality-adjusted life year (QALY) gained. In the October 2013 analysis, the base-case analysis showed that rifaximin was associated with an ICER of £20,799 per QALY gained. The company stated that the mortality predicted by the October 2013 model at 6 months (rifaximin: 6.68%; lactulose: 10.28%) reflected the trial data and CPRD data better than did the predictions from the original model. In the October 2013 model, the mortality increased to 47.66% and 55.53% respectively after 5 years. In a scenario analysis exploring the use of alternative distributions for extrapolating the time to first and subsequent hepatic encephalopathy episodes, it was noted that varying the distributions for the first episode produced a small range of ICERs (£18,909 to £19,687 per QALY gained), whereas varying the distributions for subsequent episodes produced a wider range of ICERs (£13,779 to £21,380 per QALY gained).

3.32   In the company's December 2013 base-case analysis, which comprised the October 2013 base case with a lifetime time horizon, rifaximin was associated with an ICER of £17,834 per QALY gained, compared with lactulose. In the scenario in which utility values were estimated by directly mapping SF-36 results from RFHE3001 to EQ-5D, the ICER was £29,076 per QALY gained (lifetime time horizon). In the scenarios exploring mortality (which used a lifetime time horizon and the utility values from the October 2013 analysis, that is, developed from both SF-36 and CLDQ data; see section 3.23), the ICERs ranged from £21,797 per QALY gained (mortality in overt states equal to preceding remission state) to £31,916 per QALY gained (mortality equal in all health states).

3.33   The company presented probabilistic and deterministic sensitivity analyses for its December 2013 analysis. The deterministic sensitivity analysis showed that the results were most sensitive to the incremental utility benefit associated with rifaximin. In the December 2013 base case (lifetime time horizon), the probabilistic ICER for rifaximin compared with lactulose was £18,144 per QALY gained. The company stated that the probability that rifaximin was cost effective was 95.5% if the maximum acceptable ICER were £30,000 per QALY gained. For the scenario analyses, the probabilistic ICERs were similar to the deterministic ICERs, differing by £300 to £600 per QALY gained.

3.34   In the company's November 2014 submission, it presented scenario analyses developed from the December 2013 base-case analysis. In the scenario in which the utility increment associated with rifaximin was matched to the MID for EQ-5D (that is, 0.074; see section 3.29), rifaximin was associated with an ICER of £21,331 per QALY gained, compared with lactulose. When the hospital admission rate and length of stay were adjusted based on the company's meta-analysis (mean difference, all 4 centres), the ICERs for rifaximin compared with lactulose were £7,205, £8,630 and £11,654 per QALY gained (assuming utility increments with rifaximin of 0.106, 0.074 and 0.032, respectively). In the corresponding scenarios using the meta-analysis results when the Bolton data were excluded, the ICERs were £10,063, £12,053 and £16,276 per QALY gained for rifaximin compared with lactulose (utility increments of 0.106, 0.074 and 0.032 respectively).

Evidence Review Group comments

3.35   The ERG stated that it was likely that the company's systematic review, updated after clarification, 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 company's submission. In its clarification response, the company 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 company's justification for excluding the study. However, it remained concerned about excluding neomycin from the analysis because clinical expert opinion indicated that it works in the same way as rifaximin and is sometimes

used in clinical practice, especially for people not having a liver transplant, even though it is not as well tolerated as rifaximin.

3.36   The ERG stated that the evidence submitted by the company generally reflected the decision problem adequately even though the population and comparator differed from those specified in the final scope. Whereas the scope referred to adults who have had episodes of hepatic encephalopathy, the company's submission only considered adults with chronic liver disease, excluding hepatic encephalopathy caused by acute liver disease. People with more severe liver disease (MELD score of 25 or more) were also excluded from the analysis. However, the ERG noted that the company stated that the results would apply to this population as well. The ERG was concerned about the validity of this assumption, given that the treatment effect of rifaximin 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), although the company emphasised the small numbers in this group. In addition, it noted that the study by Hassest et al. (2001), which was provided as evidence for the effectiveness of rifaximin in people with MELD scores of 20 or more, was a poor-quality descriptive study. The final scope referred to a comparison of rifaximin with lactulose, neomycin or neomycin plus lactulose, but the ERG noted that the analysis presented by the company was based on rifaximin plus concomitant lactulose compared with placebo plus 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.

3.37   The ERG indicated that RFHE3001 was a high-quality study. It noted that the treatment groups were similar in terms of baseline characteristics, although there were more men in the placebo group (67%) than in the rifaximin group (54%). The ERG stated that the outcomes assessed were appropriate and in line with those specified in the scope. Overall, the ERG considered the clinical-effectiveness data and the statistical approaches in the company's submission to be of good validity. However, it recognised that RFHE3002 was unpublished at the time of the original submission, and although assessments of Conn scores and asterixis scores were conducted to monitor hepatic encephalopathy status, only summary statistics were presented for these analyses.

3.38   The ERG reviewed the evidence from audits of clinical practice and the

company's meta-analysis of this evidence, presented in the company's November 2014 submission. It noted that the audits had some limitations, such as small sample sizes, wide confidence intervals and the potential influence of time and context (given they were observational studies). Moreover, the characteristics of the people in the audits were not known, and the ERG was uncertain how well the populations would match the people who would be treated in clinical practice, if rifaximin were recommended for widespread use in the NHS. The ERG was also uncertain whether the hospital admissions were related to hepatic encephalopathy or to any cause. While reviewing the company's meta-analysis, the ERG identified some limitations in the analysis, including discrepancies within the data, the assumption of a constant event rate, and the use of a random-effects analysis. It considered that a fixed-effects analysis might be more conservative given the small sample sizes. The ERG agreed with the company's decision to exclude multicentre data from Patel et al. (2014) and to carry out a sensitivity analysis in which the Bolton audit was excluded. It considered that the analysis in which the Bolton audit was excluded provides a better estimate for the mean difference in bed days between treatment with and without rifaximin. The ERG considered the results from the multicentre study to be published by Orr et al. in 2015; the results of this study were provided as academic-in-confidence and so cannot be reported here. The ERG highlighted that this study provided evidence from a larger population than the other audits. However, it also noted that there was limited information available on how the multicentre data had been collated and so the validity of the analysis was unknown.

3.39   In its review of the additional evidence on the long-term effectiveness of rifaximin and the effect on mortality (November 2014 submission), the ERG noted that the company did not describe any details of a systematic search to identify this evidence. It highlighted that some of the studies of long-term effectiveness identified by the company were not relevant because they did not include people with hepatic encephalopathy. The ERG considered that the study by Irimia et al. (2012) provided relevant evidence, although it noted the small population size in this study. Overall, the ERG considered that the company had provided limited additional evidence on the long-term effectiveness of rifaximin. Similarly, for the evidence on mortality, the ERG noted that 2 of the 4 identified studies were not appropriate sources for decision-making because they did not include people with hepatic encephalopathy. The ERG stated that the other 2 studies – Sharma

et al. (2013) and Neff et al. (2012) – provided evidence to support a mortality benefit associated with rifaximin for up to 3 years.

3.40 The ERG was satisfied with the company'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 company'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 people using rifaximin with concomitant lactulose and only 8.7% taking rifaximin alone. The ERG stated that a 5-year time horizon was appropriate in the company's original model to capture the relevant costs and benefits, because at that time there was no robust evidence of a mortality effect; however, it stated that in the October 2013 analysis a lifetime time horizon would have been appropriate given that approximately 52% of people in the rifaximin arm and 44% of people in the lactulose arm were alive after 5 years. In an exploratory analysis carried out in response to the company's October 2013 analysis (after the first consultation), the ERG increased the time horizon to lifetime (40 years, when all people in the model had died) and this resulted in an ICER of £22,069 per QALY gained. In its critique of the company's analysis including the lifetime time horizon presented in the December 2013 analysis (after the second consultation), the ERG stated that the company's approach was appropriate but corrected a small mistake in the company's model that reduced the ICER to £17,681 per QALY gained.

3.41 The ERG reviewed the company's October 2013 analysis and stated that the company used different time points to censor survival times when it modelled breakthrough overt hepatic encephalopathy episodes; data censoring took place at day 168 in the company's original analysis and at day 170 in the October 2013 analysis. The ERG highlighted that censoring people at day 170 resulted in different regression coefficients when extrapolating RFHE3001 data, leading to different transition probabilities. It noted, however, that censoring at day 168 rather than day 170 in the updated analysis would only increase the base-case ICER to £21,329 per QALY gained. The ERG stated that the company should have carried out some validity tests to assess the assumption of a proportional treatment effect between rifaximin and lactulose when fitting the parametric distributions to the trial data; the company presented a test of the proportional hazards assumption in its response to the second consultation, stating that there

was no evidence of a violation of the proportional hazards assumption for treatment effect. The ERG noted that assuming a proportional treatment effect implied that people will continue to have the drug until death, and this was confirmed by the ERG's clinical experts who indicated that people were generally kept on rifaximin until death or liver transplant.

3.42   The ERG considered that the company's use of data only from the newly enrolled people in RFHE3002 to avoid potential enrichment bias when modelling subsequent overt episodes (see section 3.18) was reasonable. The ERG also stated that clinical opinion indicated that the company's approach of applying the treatment effect from RFHE3001 to model subsequent overt episodes (see section 3.18) was reasonable. The ERG stated, based on clinical expert opinion, that the company's original assumption of a constant probability of subsequent episodes over time did not reflect reality. The ERG stated that the company's approach of modelling subsequent episodes as dependent on previous episodes was a significant improvement from the original analysis. However, it was concerned that combining all subsequent episodes into 1 health state does not take into account the number of episodes and does not fully address the issues around the complexity of disease progression. The ERG noted from the scenarios presented in the company's October 2013 analysis (see section 3.31) that the choice of distribution for extrapolating hepatic encephalopathy episodes had less impact on the resulting ICERs in the October 2013 analysis than it did in the original model. However, it stated that the company should have taken further steps to assess the goodness of fit of the distributions used and that the gamma distribution should have been included for completeness; the company presented an assessment of goodness of fit in its response to the second consultation.

3.43   The ERG stated that the company did not justify using different approaches to modelling mortality, that is, using survival analysis to model mortality in the remission states and using simple proportions to estimate the probability of death in the overt states. It also stated that the company did not adequately explain how it calculated the probability of death in the overt states. It noted that the Kaplan–Meier curves were not provided for visual comparison of the different distributions used to model mortality in the remission states and stated that the company should have taken further steps to assess the goodness of fit of the distributions used to extrapolate mortality; the company provided the Kaplan–Meier curve in its response to the second consultation. The ERG also

highlighted the inconsistency in the use of RFHE3002 data in the model, in which data for all people in RFHE3002 were used to model mortality, whereas only data for newly enrolled people in RFHE3002 were included in the modelling of the time to subsequent episodes.

3.44   The ERG compared mortality from RFHE3001, RFHE3002, the CPRD data and the October 2013 model. It noted that the model overestimated mortality for the lactulose arm at 6 months (10%) compared with RFHE3001 (7%), whereas mortality estimated for the rifaximin arm at 6 months was similar to that in RFHE3001 (7%). It also noted that 2-year mortality for the rifaximin arm of the model was similar to that seen in RFHE3002 and that 5-year mortality estimated from the model showed an incremental survival benefit of 8% for rifaximin compared with lactulose. The ERG stated that clinical opinion indicated that, although the survival benefit predicted was reasonable, the overall mortality seemed low for people in both arms of the model, and also that a higher number of liver transplants would be expected among people with hepatic encephalopathy (only 1 liver transplant was reported in RFHE3001; the company considered that this was not unexpected given the exclusion criteria in the study). The ERG explored the impact of mortality on the model results, by excluding the survival benefit from the remission states only, the overt states only, and all 4 states together. This resulted in ICERs of £22,700, £26,120 and £30,200 per QALY gained respectively, which shows that mortality is still a significant driver of the results.

3.45   In its critique of the company's exploration of mortality in the December 2013 analysis, the ERG stated that it was generally satisfied with the company's approach of adopting a lifetime time horizon to incorporate a diminishing mortality benefit for rifaximin. The ERG stated that it was reasonable and clinically plausible that rifaximin affects mortality. However, it noted concerns about the clinical plausibility of the different mortality rates in the 4 health states. The ERG considered it plausible that people have a higher mortality risk during overt episodes. However, although it is also plausible that people have higher mortality risk immediately after overt episodes (that is, at the start of the subsequent remission health state), the ERG queried whether the company's approach of applying a higher mortality risk throughout the subsequent remission state was appropriate. Also, the ERG noted that the company had assumed a lower mortality risk in subsequent overt episodes compared with the initial overt

episode, but considered that it would be more plausible that people have an increasing mortality risk with increasing numbers of overt episodes. The ERG highlighted a small error in the company's economic model, and correcting this error decreased the ICERs in the company's scenario analyses by approximately £200 to £300.

3.46 The ERG was satisfied with the company's use of the 6-month probabilities to model hepatic encephalopathy-related hospital admissions rather than the monthly probabilities used in the original analysis. However, it stated that clinical opinion did not support the use of the same (aggregated) probability for the rifaximin and lactulose arms, even though the company showed that the differences between the individual probabilities were not statistically significant. The ERG stated that the more conservative approach of using the individual probabilities should have been taken and, when this was explored in a scenario analysis, the ICER increased slightly to £21,389 per QALY gained. The ERG noted that, although more people had an episode of hepatic encephalopathy in the lactulose arm than in the rifaximin arm, the rate of hospital admission for those who had an episode was higher in the rifaximin arm. Therefore, the overall effect of the costs of hospital admission on the ICER was neutralised to some extent, indicating that this was not a key driver of the cost-effectiveness results.

3.47 The ERG noted that in the November 2014 submission, the company incorporated hospital admission data from its meta-analysis of clinical audit data. The ERG highlighted that the length of stay per hospital admission in this analysis was substantially longer than what has been reported in other published studies. The ERG carried out an exploratory analysis using the results from the multicentre study to be published by Orr et al. in 2015. In this analysis, using a lifetime time horizon and assuming a utility increment with rifaximin of 0.032, rifaximin was associated with an ICER of £19,791 per QALY gained; when the utility increment with rifaximin was assumed to be 0.106, rifaximin was associated with an ICER of £12,139 per QALY gained.

3.48 The ERG considered the modelling of utility values in its critiques of the company's October 2013 and December 2013 analyses. In response to the company's October 2013 analysis, the ERG stated that it was unclear why the company used the EQ-5D utility values estimated from the condition-specific CLDQ in the model given that it was possible to incorporate values directly from

mapping the SF-36 utilities onto the EQ-5D. It was concerned that the estimated quality-of-life increment with rifaximin compared with lactulose in the remission states was in contrast to the company's original analysis in which the impact on quality of life was linked to movement between the overt and remission health states only. The company considered the October 2013 approach more appropriate, based on its re-examination of quality-of-life data from RFHE3001 after the first consultation. The ERG stated that there was uncertainty in the validity of the utility increment estimated for the rifaximin arm given that the company appeared to have measured the value in centimetres directly from the study by Sanyal et al. (2011) rather than using the actual published value of difference in least square means. It also highlighted that applying the increment to the remission states only further increased the uncertainty because the incremental value reported in the study represents the CLDQ data collected for the whole duration of treatment in the trial. The ERG stated that the utility values used in the model were a key driver of the results, given that excluding the utility increment associated with rifaximin in the remission states increased the ICER to £59,421 per QALY gained.

3.49   The ERG noted that, in the December 2013 submission, the company presented a scenario analysis in which utility values were mapped directly from SF-36 data. The ERG was generally satisfied with the methods used to prepare the unadjusted utilities, although it noted a potential bias in the baseline populations (that is, people who had an overt episode during the study had lower quality of life at baseline than those who did not) and highlighted that many of the apparent differences seen may not have been statistically significant. Moreover, the ERG highlighted a number of concerns about the baseline-adjusted utilities. The ERG was not entirely clear how the adjusted analyses had been conducted, particularly regarding any differentiation between overt and remission states, and the statistical significance of the reported results was unknown. It also stated that it considered the face validity of the adjusted results to be somewhat questionable. The ERG highlighted specific concerns about each of the 3 key utility values used in the company's December 2013 analysis:

- The origin of the utility value for the remission states in the lactulose arm was unclear.

- The estimate for the difference in utility between the remission and overt states was taken from a study of the general public, rather than from

RFHE3001.

- A utility improvement (increment) was applied to the rifaximin arm relative to the lactulose arm, and the ERG was concerned that this was applied across all health states (not just the remission states); it was also unclear on the origin and statistical validity of the estimated increment.

  The ERG presented exploratory analyses to assess the effect of altering the utility assumptions. It noted that removing the utility increment associated with rifaximin in the remission states had the largest effect, increasing the ICER for rifaximin compared with lactulose by £10,379 per QALY gained; removing the utility increment associated with rifaximin from the overt states increased the ICER for rifaximin compared with lactulose by £61 per QALY gained. The ERG also examined the sensitivity of the model to the utility decrement associated with overt states compared with the remission states (that is, how much quality of life deteriorates during an overt episode). It found that reducing this decrement by approximately 40% to 70% increased the ICER by £100 to £200 per QALY gained. The ERG emphasised that the utility values used in the economic model, and in particular the utility increment associated with rifaximin in the remission states, were key drivers of the cost-effectiveness results.

3.50 The ERG reviewed the evidence for the minimum important difference (MID) in utility scores and considered the company's analysis in which the rifaximin utility increment was the same as the MID. It noted that studies included in the analysis of MID by Walters and Brazier (2005) did not include people with liver disease or hepatic encephalopathy, and so the reported average MID might not apply for people with this condition. The ERG also emphasised the wide range of values for the MID reported by this study (see section 3.29). It noted that an increment of 0.032 falls within this range, and therefore stated that it could not conclude which utility increment would be the most appropriate based on this evidence.

3.51 The ERG was satisfied with the calculation of costs in the model. It noted differences in the cost of outpatient attendance for hepatic encephalopathy events in people who did not need hospital admission between the original and October 2013 analyses, but the company explained that these resulted from an error in the original submission that was corrected in the October 2013 analysis.

The ERG noted that the company did not include costs for adverse events because they were comparable between the rifaximin and placebo groups in the pivotal trial, but stated that including relative risks (or risk difference) and 95% confidence intervals for each adverse event would have strengthened this justification. However, the ERG also stated that including adverse events in the costs and QALY calculations would not have a significant impact on the ICER.

3.52 Full details of all the evidence is in the committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rifaximin, having considered evidence on the nature of hepatic encephalopathy and the value placed on the benefits of rifaximin by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee heard from the patient expert that hepatic encephalopathy has a profound impact on people's daily activities and quality of life, with symptoms including personality changes, reduced levels of consciousness and altered neuromuscular activity, with a resulting impact on caregivers. The Committee noted comments from consultation that treatment with rifaximin would improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden. It heard from the clinical and patient experts that avoiding hospital admissions is very important for people with hepatic encephalopathy and may be beneficial for their mental health, as well as the health of their carers and families. The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families and carers.

4.2 The Committee considered the clinical management of hepatic encephalopathy. The Committee heard from the clinical experts that after an episode of overt hepatic encephalopathy, it was important to prevent or reduce the recurrence of overt episodes, which may be fatal. It heard that rifaximin was the only licensed treatment available to prevent episodes of hepatic encephalopathy. The Committee heard from the clinical experts that there are few treatment options for this condition, and that current standard practice includes treatment with lactulose, or other laxatives, primarily because hepatic encephalopathy episodes are often triggered by constipation. The clinical experts stated that neomycin was not used routinely in clinical practice because of the significant toxicity associated with its long-term use (in particular, its association with deafness). The Committee concluded that neomycin was not an appropriate comparator for this appraisal, and that rifaximin should be compared with lactulose alone. However, the Committee also heard that lactulose was not well tolerated; when used in large doses it can cause diarrhoea, although doses are titrated to improve

their tolerability. The patient expert emphasised that lactulose treatment is considered undignified and there is a need for alternative treatment. The patient expert also emphasised that adding rifaximin to current treatment with lactulose may result in reduced doses of lactulose, which may improve adherence to treatment. The Committee recognised the need for alternative treatment options for preventing episodes of overt hepatic encephalopathy.

Clinical effectiveness

4.3   The Committee discussed the pivotal RFHE3001 trial. The Committee was satisfied that the trial was well conducted and that relevant outcomes were assessed in line with the scope of the appraisal, including health-related quality of life using the Chronic Liver Disease Questionnaire (CLDQ) and SF-36 questionnaire. However, the Committee noted that mortality was not reported because the data were not considered mature enough to assess the effect of rifaximin on mortality. The Committee noted that people with more severe liver disease (Model End Stage Liver Disease [MELD] score of 25 or more) were excluded from the trial, but that the company had suggested the trial results may apply to this group. It noted the Evidence Review Group's (ERG) concerns that this was unlikely because the effectiveness of rifaximin in the subgroup of people with MELD scores of 19 to 24 was not statistically significantly better than placebo, although the Committee recognised that this subgroup comprised only 26 of the 299 people in RFHE3001. The Committee was aware that 91.4% of people in the rifaximin arm and 91.2% of people in the placebo arm had concomitant lactulose and queried whether this reflected normal practice. The clinical experts confirmed that this was in line with UK clinical practice and there was limited evidence on the efficacy of rifaximin monotherapy (8.6% of people in RFHE3001). The Committee concluded that RFHE3001 was appropriately conducted and relevant to UK clinical practice.

4.4   The Committee examined the clinical-effectiveness data from RFHE3001, which compared rifaximin with placebo. The Committee noted that there was a statistically significant reduction in the risk of a breakthrough episode of overt hepatic encephalopathy compared with placebo for the intention-to-treat (ITT) population (see section 3.6). It also noted that rifaximin was associated with statistically significant reductions in the risks of hepatic encephalopathy-related

hospital admission and any increase from baseline in Conn scores. However, the improvements in asterixis score and venous ammonia levels were not statistically significant, and the differences between the rifaximin and placebo arms in changes in CLDQ fatigue scores, SF-36 scores and Epworth Sleepiness Scale scores were minimal (see section 3.6). The Committee considered the mode of action of rifaximin. It heard from the clinical experts that apart from reducing blood ammonia levels, rifaximin also influenced endotoxin production and reduced systemic inflammation, which plays an important role in the development of hepatic encephalopathy. The Committee questioned whether this was in line with the proposed mode of action of rifaximin, but the company explained that the pathogenesis of hepatic encephalopathy remains speculative and is an area of ongoing research. The clinical experts stated that both the ammonia-lowering and endotoxin-lowering properties of rifaximin were relevant in producing a treatment effect. The Committee also discussed RFHE3002, which was an open-label, follow-up study to assess the long-term safety and tolerability of rifaximin. It noted that not all people from RFHE3001 continued in RFHE3002, which may be a potential source of selection bias. RFHE3002 provided only exploratory effectiveness data. The Committee concluded that rifaximin was effective in preventing episodes of overt hepatic encephalopathy in the trial population.

4.5   The Committee considered whether the effectiveness of rifaximin was maintained during long-term treatment. It understood that there is limited evidence on the long-term effects of rifaximin. The Committee noted that although RFHE3002 was of 2-years' duration, the lack of a control arm made interpretation of the effect of rifaximin difficult. However, it saw that the time between hepatic encephalopathy episodes progressively decreased as the number of episodes increased. The Committee considered that there was no evidence in RFHE3001 and RFHE3002 that rifaximin alters the natural history of liver disease or hepatic encephalopathy and noted comments received during consultation from the clinical expert that the greatest benefit of the drug may be obtained in the first 3 months of treatment. It noted that further studies exploring the long-term efficacy of rifaximin were presented in the company's November 2014 submission, and considered that these studies provided limited additional evidence of the long-term effects of the drug. The Committee heard from the clinical experts that although there is little trial evidence, in their clinical experience (based on 5 years of rifaximin use in clinical practice) rifaximin may

provide long-term benefits. It concluded that the long-term benefits associated with rifaximin were uncertain, but that the greatest benefits would be expected in the early stages of treatment.

4.6   The Committee considered the adverse event profile associated with rifaximin in RFHE3001. It noted that hepatic encephalopathy adverse events leading to study discontinuation occurred less frequently in the rifaximin group than in the placebo group. However, anaemia, peripheral oedema, pyrexia, arthralgia and dizziness occurred more frequently in the rifaximin group than in the placebo group (see section 3.8). The Committee noted that approximately 56% of people had severe adverse events in RFHE3002. The Committee also noted from the Medicines and Healthcare Products Regulatory Agency (MHRA) public assessment report that cases of diarrhoea associated with Clostridium difficile have been reported with the use of rifaximin. It understood that this was a potential ongoing safety concern with the use of antibacterial agents including rifaximin. It heard from the company that the MHRA public assessment report stated that there were no new safety concerns with rifaximin and the benefit–risk profile was considered to be positive. It noted the patient expert's statement that the potential side effects of rifaximin were considered to be more tolerable than the physical and psychological side effects associated with current treatment (such as diarrhoea associated with lactulose treatment), which have a detrimental effect on quality of life for people with the condition and their carers. The Committee concluded that the current evidence indicates that rifaximin has an acceptable adverse event profile.

4.7   The Committee considered evidence from clinical audits of rifaximin, provided by the clinical expert in response to the second consultation and by the company in its November 2014 submission. The Committee highlighted that these retrospective observational studies were challenging to interpret. It noted that outcomes were compared before and after starting treatment with rifaximin and therefore could be influenced by many factors. In particular, when rifaximin treatment was started any of a number of factors may also have changed, which could have contributed to the benefits seen with rifaximin; for example:

- level of alcohol consumption (in people with alcohol-related liver disease)

- level of care (because of the introduction of a specialist hepatologist)

- use of lactulose.

  The clinical experts described steps taken to minimise the effects of these factors, but the Committee considered that confounding factors were likely to have influenced the results and that the benefits could not be attributed to the use of rifaximin alone. The Committee concluded that the audits provided informative supporting evidence, in particular about hospital stays, but considered the pivotal randomised controlled trial (RFHE3001) to be the main source of evidence for determining the clinical efficacy of rifaximin.

4.8 In its review of the evidence from clinical audits, the Committee considered the effect of rifaximin on hospital admissions. It understood that the analyses of hospital admissions included all emergency admissions, and therefore it noted that the results may be influenced by admissions unrelated to hepatic encephalopathy. In light of this and the possible confounding factors (see section 4.7), the Committee considered that the results were very uncertain. The Committee noted that the results suggested that treatment with rifaximin reduces the duration of hospital stay, compared with treatment without rifaximin. It heard from the clinical expert that this may be because people admitted with an episode of hepatic encephalopathy while taking rifaximin tend to have less severe symptoms than people taking lactulose. The Committee acknowledged that the results from the audits were subject to uncertainty, but concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay.

Cost effectiveness

4.9 The Committee considered the company's economic model and the ERG's critiques of the company's submissions. It noted that the company presented 4 iterations of its model over the course of the appraisal (referred to in this document as the 'original', 'October 2013', 'December 2013' and 'November 2014' analyses; see section 3.16). It accepted the exclusion of neomycin from the analysis because it was not routinely used in clinical practice. The Committee noted that in the October 2013 analysis the company amended the way it estimated the risk of subsequent episodes and that this model assumed that the

risk of subsequent hepatic encephalopathy episodes depended on time since the first episode. The Committee was aware that all subsequent episodes were combined in 1 health state (the subsequent overt state), thereby not reflecting the number of episodes. However, it noted that including more health states for subsequent episodes would increase the complexity of the model and would be difficult to populate with the current evidence base. The Committee therefore concluded that, although the number of episodes was not considered and the company's original analysis oversimplified the nature and course of the disease, the October 2013 model was an improvement on the original analysis and was appropriate for decision-making.

4.10　The Committee discussed the most appropriate time horizon for the model. It noted that in the company's submissions, a number of different time horizons were presented, including 5-year, 10-year and lifetime. It also noted that in the October 2013 analysis 52% of people treated with rifaximin and lactulose (referred to in this document as the rifaximin arm) and 45% of people treated with placebo and lactulose (referred to in this document as the lactulose arm) were predicted as being still alive in the model after 5 years. The Committee was aware that the NICE reference case (Guide to the methods of technology appraisal 2013) indicates a preference for a lifetime time horizon when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life. It noted that the ERG had conducted an exploratory analysis based on the company's October 2013 model, incorporating a lifetime time horizon of 40 years. It also noted that the company incorporated a lifetime time horizon (of 42 years) in its December 2013 and November 2014 analyses, in response to a request from the Committee. The Committee heard from the clinical expert that people with hepatic encephalopathy would not survive for up to 40 years because of their underlying liver cirrhosis; the Committee noted that a time horizon of 40 years did not imply that all people survived for 40 years, and heard from the company that most people in the model died within the first 5 to 10 years. It considered that the prolonged survival in the model could be a result of extrapolating outcomes using the log normal distribution, which has a long tail and could lead to implausible survival results, although few people remained alive in the later stages of the model. The Committee concluded that the company's choice of a 5-year time horizon in its October 2013 analysis was not in line with the NICE reference case, and that the lifetime time horizon presented in the December 2013 and November 2014 analyses was appropriate.

4.11 The Committee discussed the assumptions used to model clinical outcomes. It noted that, in its October 2013 analysis (and all subsequent analyses), the company used data from RFHE3001 only to model breakthrough overt hepatic encephalopathy episodes for both arms of the model, rather than the combined data set from RFHE3001 and RFHE3002 used to model the rifaximin arm in the original analysis. The Committee also noted the ERG's comment that data censoring when modelling time to first breakthrough overt episode was inconsistent between the October 2013 analysis and the original analyses, that is, at day 170 and day 168 respectively. However, it considered the October 2013 analysis at day 170 to be more appropriate given that the clinical study report for RFHE3001 reports data censoring at day 170. It also noted that the company included only newly enrolled people from RFHE3002 when modelling subsequent overt episodes to avoid potential enrichment bias from rollover and crossover people who did not have an overt episode in RFHE3001. The Committee was satisfied with this approach given the evidence presented by the company showing that time to first breakthrough overt episode was not statistically significantly different between the RFHE3002 subgroups (rollover, crossover and newly enrolled people; see section 3.19). The Committee noted that there was less variation in the incremental cost-effectiveness ratios (ICERs) from the October 2013 analysis (see section 3.31) than those of the original analysis when different distributions were used to model time to first breakthrough and subsequent overt episodes. The Committee concluded that the company's modelling of hepatic encephalopathy episodes in the October 2013 and subsequent submissions was appropriate.

4.12 The Committee considered the effect of rifaximin on hospital admissions in the model. It understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose, and noted that comments from consultation supported this. The Committee was aware that, in the October 2013 and December 2013 submissions, the company assumed that 53% of episodes of hepatic encephalopathy led to admission, with a length of hospital stay of 5 days per admission, in both arms of the model. It also saw that, in the November 2014 submission and ERG review, these assumptions were varied to match the number of hospital admissions and bed days seen in clinical audits. To do this, the company identified values for the length of stay in hospital and the probability of hospital admission so that the model simulated the results of the audits. The Committee therefore discussed the validity of using the audit

data, and the most appropriate estimates for the length of stay and probability of hospital admission:

- It noted that the results of the audits were uncertain, and that the admissions seen in the audits may have included admissions unrelated to hepatic encephalopathy (see section 4.8); the Committee therefore considered that it was not appropriate to use artificially identified values to match the audits in this way.

- Considering the length of stay, the Committee noted that Hospital Episode Statistics for encephalopathy admissions suggested that the mean stay is around 17 days, although this estimate was based on surrogate disease codes. The Committee noted that in the November 2014 submission, the assumed lengths of stay (20 to 30 days; see section 3.25) were substantially longer than had been assumed previously. It heard from the clinical experts that stays of approximately 5 to 10 days would be clinically plausible. The Committee considered that it would be more appropriate to use the lengths of stay seen in the multicentre audit to be published by Orr et al. in 2015 (provided as academic-in-confidence and so cannot be reported here).

- The Committee then considered the probability of hospital admission in the model. It noted that in the October 2013 and December 2013 analyses, the company used the same (aggregated) probability for hepatic encephalopathy-related hospital admissions in the model, because the difference between the rates of hospital admissions for the rifaximin and placebo groups was not statistically significant. The Committee considered this approach to be selective and that the individual rates would have been more appropriate, although it noted that the impact on the ICER was minimal (see section 3.46). It noted in the November 2014 submission, that the company assumed the probability of admission was 100%, to simulate the results of the audits; the Committee considered that this was not appropriate, and that it would be more appropriate to use the trial data for the probability of admission than this artificial value. The Committee recalled comments from the clinical and patient experts that, if possible, many people with hepatic encephalopathy would prefer to be treated at home rather than in hospital.

  The Committee noted that assuming the length of hospital stay associated

with rifaximin was shorter than with lactulose reduced the ICER for rifaximin compared with lactulose (see section 3.34), but that the effect on the ICER would be smaller if its preferred assumptions (that is, the probability of hospital admission from the clinical trial and the lengths of stay from the multicentre audit) were used. The Committee concluded that it was plausible that rifaximin may reduce the length of stay for admissions related to hepatic encephalopathy, but that the methods used by the company and the ERG to simulate the clinical audits were not appropriate.

4.13 The Committee considered how the company included adverse events in the model. The Committee noted that adverse events were excluded from the cost calculation on the basis that there were no statistically significant differences between the treatment arms in RFHE3001 and there was limited evidence for disutilities associated with the adverse events. It heard from the clinical experts that adverse events were minimal and primarily related to lactulose use. The ERG stated that including adverse events was not likely to have a large impact on the cost-effectiveness results. The Committee was uncertain of the impact on the ICER and concluded that an attempt should have been made to capture some of the differences in the costs of adverse events between the rifaximin and lactulose arms.

4.14 The Committee considered the approaches taken to estimate the utility scores for use in the model. It noted that in the October 2013 analysis, utilities were based on quality-of-life data collected from RFHE3001, derived using both SF-36 and CLDQ scores. It expressed several concerns about this approach. In particular, it considered that including CLDQ scores in the mapping process unnecessarily introduced uncertainties, was associated with missing data, and was based on a post-hoc analysis of CLDQ. It highlighted that the post-hoc analysis identified statistically significant differences that were not seen in the per-protocol analysis. The Committee also expressed further concerns relating to the choice of a single, linear regression equation, the imputation of missing data, and the use of overall scores rather than individual domains. The Committee did not accept the company's views that the high variance in SF-36 scores supported the use of the CLDQ, or that the SF-36 was necessarily influenced substantially more than the CLDQ by issues with recall. The Committee noted the company's scenario analysis in which utilities were derived from SF-36 data only (December 2013 submission). Although it was aware that the company retained a

preference for the analysis that used both SF-36 and CLDQ data, the Committee considered that the approach based on SF-36 data only was more appropriate. The Committee concluded that the most appropriate approach for deriving the utility scores was the analysis based on SF-36 data only.

4.15   The Committee considered the utility scores that were used in the model. The Committee noted that the estimates in the October 2013 and December 2013 analyses implied a quality-of-life improvement (utility increment) associated with rifaximin in the remission states. It understood that scenario analyses presented by the ERG in which the utility increment for rifaximin was omitted showed that the model results were highly sensitive to this value. The Committee heard from the clinical expert that remission (in particular, Conn score 1) is also known as minimal hepatic encephalopathy and people still have mild neurological abnormalities, reversal of the sleep-wake cycle and reduced quality of life. It heard that lower Conn scores do not indicate normal quality of life, although a Conn score of 0 is defined as 'no personality or behavioural abnormality detected'. The Committee heard from the clinical experts that rifaximin improves quality of life and could enable people to return to their normal activities with less dependence on carers. The Committee considered that it was plausible that rifaximin could improve quality of life in the remission states, and understood that the model results were highly sensitive to the size of improvement.

4.16   The Committee reviewed in detail the estimates for the utility increment associated with rifaximin presented by the company. The Committee expressed concerns about the face validity of the utility increment estimated using both CLDQ and SF-36 data (0.106), noting that this was larger than the difference between the overt and remission states in the October 2013 analysis. The Committee recognised that rifaximin may improve quality of life in the remission states (see section 4.15), and given that this improvement could be seen in clinical practice, the associated utility increment could represent a minimum important difference (MID) in utility value. The Committee noted evidence presented by the company in its November 2014 analyses (which explored MIDs in EQ-5D values across a range of conditions), from which it had suggested applying a utility increment of 0.074 to match the MID. The Committee noted the wide range of estimates for MID presented, and understood that that these were from a number of different conditions (none of which were related to hepatic encephalopathy) and were therefore difficult to interpret. Taking into account

limitations of the evidence on MIDs and the analysis based on both CLDQ and SF-36 data (see section 4.14), the Committee considered that a utility benefit of 0.106 or 0.074 in the remission states was not reliable. The Committee considered that the estimated utility increment derived using SF-36 data only (0.032) was more appropriate, but was aware of the uncertainties surrounding this value. The Committee understood that the differences between placebo and rifaximin seen in the baseline-adjusted analysis of SF-36 were not statistically significant, and that the utility increment used in the company's economic model reflected the highest value for the difference between rifaximin and placebo that had been seen in this analysis. Given that it had heard that the greatest benefits associated with rifaximin may be obtained in the first 3 months, the Committee considered that incorporating a more conservative value such as that seen at month 3 in the baseline-adjusted analysis might have been informative. Furthermore, noting its conclusion that the long-term effectiveness of rifaximin is uncertain (see section 4.5), the Committee considered that even if people did initially experience the maximal utility increment as modelled by the company, it was uncertain whether this increment would be maintained at that value throughout the full 42-year time horizon of the economic model. The Committee concluded that it was plausible that rifaximin could be associated with a utility increment in the remission states and that there are substantial challenges in identifying the most plausible value for this utility increment. It further concluded that the increment could be lower than the highest value for the difference between rifaximin and placebo in the baseline-adjusted analysis of SF-36 (0.032) and could plausibly decrease further during long-term treatment, but that the most appropriate utility increment for decision-making was 0.032.

4.17 The Committee considered the other utility estimates derived using SF-36 data only, presented in the company's December 2013 submission. It noted that the ERG was unclear of the origin of the utility value for the remission states in the lactulose arm (0.568), and heard from the company that this was the average baseline utility score for all people in the analysis. The Committee also noted that the difference in utility between the remission and overt states (0.286) was taken from a survey of the general population using standard gamble methods, whereas the time trade-off method was used previously. However, it understood from the ERG that the results of the model were not sensitive to this and it considered the company's utility estimate to be broadly reasonable. The Committee understood that there are substantial challenges in capturing

quality-of-life evidence in people with hepatic encephalopathy, but concluded that the utility estimates had captured the reduced quality of life associated with hepatic encephalopathy.

4.18   The Committee considered the plausibility of the mortality estimates in the company's models. It noted that all of the models presented by the company predicted that rifaximin was associated with a mortality benefit. It recognised that this mortality benefit came from avoiding overt episodes (which were associated with a higher mortality rate than the remission states) rather than an explicit survival benefit applied to the rifaximin arm. The Committee considered whether this was clinically plausible. It noted that no differences in mortality were seen between rifaximin and placebo in RFHE3001. The Committee noted that data showing a mortality benefit associated with rifaximin were presented by the company in its October 2013 submission. However, it was concerned that these data may not provide robust evidence because they were based on a retrospective observational study (Neff et al. 2012) and that mortality was substantially higher than seen in RFHE3001. The Committee also considered that the finding that mortality was higher with rifaximin plus lactulose than with rifaximin alone was unexpected. However, the Committee heard from the clinical expert that it was plausible for rifaximin to affect mortality and that the modelled difference between rifaximin and lactulose seemed reasonable; the clinical expert reported positive experiences with people treated for up to 5 years. The Committee concluded that although a mortality benefit had not been seen in RFHE3001, it was willing to accept that an initial mortality benefit with rifaximin resulting from a reduction in overt hepatic encephalopathy episodes was plausible. However, it considered that the magnitude of the effect is uncertain and that it is likely to decrease over time.

4.19   The Committee considered how mortality had been modelled by the company, noting from ERG scenario analyses (see section 3.44) that the model was sensitive to mortality estimates:

- It noted that, in the original analysis, approximately 50% of the modelled population died over a 6-month period compared with 7% (21 deaths) in RFHE3001, and agreed this was unrealistic.

- It noted that, in the October 2013 analyses, mortality was similar to that in the Clinical Practice Research Datalink (CPRD), and in RFHE3001 and

RFHE3002. However, the Committee was concerned that the model predicted a difference of 3.6% in the risk of mortality with rifaximin compared with lactulose during the first 6 months of the model and a difference of up to 8% over the 5 years. In addition, it heard from clinical experts that the time to subsequent overt hepatic encephalopathy episodes decreases as the number of episodes increases, and the risk of death from other causes increases with disease progression, but noted that the model predicted that the mortality benefit with rifaximin increased over the first 5 years.

- It noted that, in the December 2013 analyses, which used a lifetime time horizon, the mortality benefit associated with rifaximin decreased over time. However, it also noted that it took approximately 20 years for the mortality benefit to decrease to the level predicted at 6 months.

- It considered the company's scenario analysis (see sections 3.23 and 3.32) which showed that reducing the mortality benefit associated with rifaximin (by reducing the differences in mortality rate between the different health states in the model) increased the ICER. It agreed that the mortality benefit with rifaximin may have been overestimated in the October 2013 and December 2013 analyses. However, it also agreed that the most extreme scenario, in which there was no mortality benefit with rifaximin, and which increased the ICER by approximately £14,000 per QALY gained (see section 3.32), was not plausible.

- It noted that in the November 2014 submission, the company provided additional evidence on the effect of rifaximin on mortality. It noted that this evidence was of interest, but there were a number of uncertainties, in particular about the similarity of the study populations to people for whom rifaximin is licensed. The Committee therefore considered that the additional studies did not provide sufficient evidence to affect its decision.

  The Committee concluded that the most plausible mortality assumption would lie between the company's base case and the extreme scenario in which there was no mortality benefit associated with rifaximin.

4.20 The Committee discussed the effects of the uncertainties about the mortality and utility assumptions and hospital admissions on the results of the economic model. It noted that none of the ICERs presented took into account all of the

uncertainties and all of the Committee's preferred assumptions. It noted that in the scenario based on its preferred method for calculating utility, the ICER was £29,000 per QALY gained for rifaximin compared with lactulose (see section 3.32). However, it noted that if the utility increment associated with rifaximin in the remission states were lower than the estimate of 0.032, or reduced over time, the ICER for rifaximin would increase (see section 3.48). In addition, the Committee noted that the mortality benefit of rifaximin in the model was likely to be overestimated, and that accounting for this by reducing the mortality benefit for rifaximin would increase the ICER (see section 4.19). However, the Committee also noted that incorporating a reduced length of hospital stay for rifaximin, compared with lactulose, would reduce the ICER. The Committee concluded that, on balance, the most plausible ICER was likely to be close to the top end of the range normally considered cost effective.

4.21 The Committee acknowledged that with an ICER close to the top end of the range normally considered cost effective, it needs to identify an increasingly strong case for supporting the technology as an effective use of NHS resources, taking into account:

- whether the change in health-related quality of life has been adequately captured

- the innovative nature of the technology

- whether the technology is a life-extending treatment at the end of life

- aspects that relate to non-health objectives of the NHS and

- the degree of certainty around the ICER.

    The Committee noted the company's comments regarding the innovative nature of rifaximin. The company stated that rifaximin was expected to offer a step change in the management of hepatic encephalopathy by significantly reducing breakthrough episodes and hospital admissions, while maintaining health-related quality of life. The Committee heard from the clinical experts that the use of rifaximin could potentially reduce the number of people on the liver transplant list, which would reduce the burden of expensive procedures on the healthcare system. The patient expert also emphasised that availability of rifaximin would reduce the doses of lactulose given to people,

thereby improving their wellbeing. The Committee noted that preventing episodes of hepatic encephalopathy was a new indication for rifaximin, and that it is well tolerated, but considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families and carers, including loss of income. The Committee heard from the clinical and patient experts that people with hepatic encephalopathy may be considered vulnerable adults, and have a substantial unmet need. It heard from the clinical expert that symptoms of hepatic encephalopathy are similar to dementia and can also cause features of Parkinson's disease. People develop depression, wander at night, are unable to work and need constant supervision either from family or professional carers. The Committee agreed that the costs associated with constant care from family members and professional carers could not be built into the model and factoring them in would reduce the ICER, although it noted that it had not been presented with any evidence on the effect of rifaximin on families and carers.

4.22 With these factors in mind, the Committee considered whether rifaximin reflected a cost-effective use of NHS resources. Although it understood that the most plausible ICER was at the top end of the range that is normally considered acceptable and was subject to a number of uncertainties, it was also aware of the important unmet medical need in this group of vulnerable people for whom there are few treatment options. It also acknowledged the innovative aspects of this treatment. Consequently, the Committee concluded that rifaximin could be considered a cost-effective use of NHS resources for reducing the recurrence of episodes of overt hepatic encephalopathy in people aged 18 years or older.

4.23 The Committee considered whether the appraisal might be affected by any issues relating to equality. It noted comments received during consultation from the clinical expert that people with hepatic encephalopathy should be considered vulnerable adults. The Committee understood that this condition can have a substantial disabling effect, but considered that its recommendations do not discriminate on the basis of any characteristics protected under the equalities legislation.

5 Implementation

5.1   Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2   The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3   When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient is at risk of recurrence of episodes of overt hepatic encephalopathy and the healthcare professional responsible for their care thinks that rifaximin is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
General Practitioner, West Coker Surgery, Somerset

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley

Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital, Cardiff

Tracey Cole

Lay Member

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

John Dervan

Lay Member

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Dr Martin Duerden

Assistant Medical Director, Betsi Cadwaladr University Health Board, North Wales

Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Christopher Earl

Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh

Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal
Hospital for Children

Dr Paul Hepple

General Practitioner, Muirhouse Medical Group

Professor John Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Emeritus Professor of Statistics, Keele University

Professor Steven Julious

Professor of Medical Statistics, University of Sheffield

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Warren Linley

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor
University

Professor Jonathan Michaels

Professor of Clinical Decision Science, University of Sheffield

Dr Malcolm Oswald

Lay Member

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust and Metropolitan Borough Council

Dr Mohit Sharma
Consultant in Public Health, Public Health England

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray Smith
Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie
Lay Member

Charles Waddicor
Chief Executive, NHS Berkshire West

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Nwamaka Umeweni and Ian Watson
Technical Leads

Raisa Sidhu and Melinda Goodall
Technical Advisers

Kate Moore
Project Manager

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7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG):

- Bacelar M, et al. The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy: A critique of the submission from Norgine, April 2013

PenTAG also prepared reviews of the company's second and third evidence submissions (October 2013 and December 2013). A review of the company's final submission was prepared by Southampton Health Technology Assessments Centre (SHTAC; November 2014).

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Companies were also invited to make written submissions. Professional or expert and patient or carer groups, and other consultees, had the opportunity to give their expert views. Companies, professional or expert and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Company:

- Norgine

Professional or expert and patient or carer groups:

- British Liver Trust

- British Infection Association

- British Society of Gastroenterology

- Royal College of Nursing

- Royal College of Pathologists

- Royal College of Physicians

Other consultees:

- Department of Health

- South Essex Primary Care Trust Cluster

- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service

- Department of Health, Social Services and Public Safety for Northern Ireland

- Healthcare Improvement Scotland

- Foundation for Liver Research

- National Institute for Health Research Health Technology Assessment programme

- Peninsula Technology Assessment Group (PenTAG)

- Southampton Health Technology Assessment Centre

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on rifaximin by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Sulleman Moreea, consultant Gastroenterologist and Hepatologist, nominated by the British Society of Gastroenterology – clinical expert

- Dr Debbie Shawcross, Senior Lecturer and Honorary Consultant in Hepatology, nominated by Norgine – clinical expert

- Andrew Langford, Chief Executive of the British Liver Trust, nominated by British Liver – patient expert

Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and

comment on factual accuracy.

- Norgine

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