NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Rifaximin for preventing episodes of overt hepatic encephalopathy

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Comments received from consultees

Consultee	Comment	Response
British Association for the Study of the Liver	**Comments submitted on behalf of members of BASL (British Association for the Study of the Liver)** 1. Impact of rifaximin therapy on quality of life for the patients and their carers: Anecdotal, but we do have positive reports from both patients and carers 2. Impact of rifaximin therapy on admissions to hospital: Although we have small numbers so far, and in some patients it is too early to comment on this, we have noted a reduction in admissions of between 50 - 70% approximately in patients commenced on rifaximin over the last year. For example, one patient who had had 10 admissions in the preceding year has only had 3 admissions this year. We believe that so far, in carefully selected patients, there is a noticeable improvement in many cases once on Rifaximin. Therefore we would value it being funded appropriately. [redacted] We have been using Rifaximin in patients with overt hepatic encephalopathy for many years. Our use has progressively increased with the clinical benefit in quality of life for the majority of patients and their families. We have audited our practice and demonstrated a reduction in emergency admissions in 25 patients who we were able to follow up for a year after commencing Rifaximin. This has been of immense benefit to our patients [redacted] We are a busy regional non transplant unit. I do not think rifaximin should be first line but has an important role in a selected group of patients with difficult to control/manage hepatic encephalopathy and has been a miracle drug in a few selected group of patients in both preventing readmissions, getting out of hospital and improving quality of life. All prescriptions have been hepatology consultant initiated. Experience attached. [redacted] Rifaximin is clearly helpful to some of my patients with chronic encephalopathy but my evidence is anecdotal. I have seen a reduction in hospital readmissions with its use and also clear improvement in quality of life. [redacted] We are based in Wrexham in North Wales. About 3 years ago we tried Rifaximin in 2 patients with excellent results.	Thank you for your comments. The Committee noted comments that treatment with rifaximin could improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden (see section 4.1 of the final appraisal determination [FAD]). The Committee considered that rifaximin could improve quality of life, although acknowledged that there are substantial challenges in identifying the size of this effect. The Committee concluded that rifaximin was effective in preventing episodes of overt hepatic encephalopathy in the trial population, although the long-term benefits associated with rifaximin were uncertain. The Committee considered in detail the effect of rifaximin on hospital admissions. It acknowledged that the findings from clinical audits of rifaximin were subject to uncertainty, but concluded that rifaximin is likely to reduce hospital admissions and may shorten the length

Consultee	Comment		Response
	Dose was 400mgs tds as was before Targaxan was launched so was ordered from overseas. First patient was an elderly lady but usually independent with decompensated liver disease. Ascites and recurrent encephalopathy were her main problems and she was in hospital for long periods where she would then pick up infections too. As soon as we started the Rifaximin she was home within the week and we were able to only admit for paracentesis management. She and her family were thrilled with the drug as it restored her mental state back to normal and allowed her to go home which she was desperate for. This allowed her to have a great quality of life for the next 18 months before she passed away and reduced amount of time in hospital. Second was a gentleman also with decompensated liver disease but the encephalopathy was his main problem. He would often end up being admitted as an emergency after being found collapsed at home by neighbour or family when they visited. This caused him and his family great distress. We added Rifaximin and he too improved dramatically and was able to go home quickly. He had no further episodes which he was happy about seeing as he lived alone. He was transplanted about 8 months later. Both of these were also taking lactulose regularly and were compliant with medication but adding in the Rifaximin allowed them both to have a dramatic improvement in quality of life. They both lived alone so safety was also a priority. [redacted] Although patients with chronic incapacitating encephalopathy are relatively infrequent I certainly have current experience with two patients in whom rifaximin has been critical in keeping them out of hospital and less dependent on family carers. From my limited perspective, it is a valuable additional medication, especially if lactulose or other conventional approaches have failed. [redacted]		of hospital stay (see FAD section 4.8).
British Liver Trust	Section 1 (Appraisal Committee's preliminary recommendations)	As per previous submissions this treatment offers a significant improvement in the quality of life for people with, and affected by, hepatic encephalopathy - the British Liver Trust hopes that the committee will move to approving rifaximin-a as a treatment for HE.	Thank you for your comments. The Committee understood that hepatic encephalopathy has a profound impact on patients' daily activities and quality of life, with a resulting impact on caregivers. The Committee noted comments that treatment with rifaximin could improve quality of life,

Consultee	Comment		Response
	Section 4 (Consideration of the evidence)	As the Committee acknowledges hepatic encephalopathy has a far-reaching effect on family and carers - I call on the committee to have this in mind - especially as current treatment can be so humiliating and dehumanising for some people with HE.	and reduce morbidity and carer burden (see FAD section 4.1). The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families (see FAD section 4.21).
Liver4Life	Section 4 (Consideration of the evidence)	The Appraisal Committee has stated that it is interested in receiving comments on the following: Has all of the relevant evidence been taken into account? In the opinion of Liver4Life they have not. Patient experiences are about more than the effects of lactulose, and the effect that an episode of HE can have on a family can be devastating. My own Father had episodes of HE in 2007/8 which brought my whole family to a standstill. I had to take time off from work to look after him as my mother 'couldn't cope' with his unpredictable nature. This involved expensive journeys from Bournemouth to Coventry two or three times a week. I have also included statements from two other patients below who have experienced HE first hand. December 2013 [redacted] As a result of my condition I also have been diagnosed with	Thank you for your comments. The Committee noted comments that treatment with rifaximin could improve quality of life, and reduce morbidity and carer burden (see FAD section 4.1). The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families (see FAD section 4.21). The Committee understood that there are substantial challenges in capturing quality of life evidence in people with hepatic encephalopathy, but concluded that the estimates provided had captured the reduced quality of life

Consultee	Comment		Response
		oesophageal varices, enlarged spleen, osteoporosis, IBS, liver cirrhosis and most recently have been showing symptoms of Hepatic Encephalopathy. I was prescribed Rifaximin just under a year ago now when I began experiencing changes in my general wellbeing. My main initial complaint was the uncontrollable feeling of being 'on edge' and tiredness as I wasn't able to sleep at night and therefore found myself extremely fatigued and sleepy during the day. This slowly progressed and my ability to concentrate on simple day to day things became increasingly difficult as I would forget things and be confused with basic communication and tasks, which would make me so frustrated as it was not like me to be 'intellectually' that way. It was a scary time as it felt as though my normal mental ability and retention was diminishing and I would get moody because of the frustration as to the reasons why this was happening. Ultimately, these symptoms gradually began to have a knock on effect on my life. My immune system was weakened by the exhaustion and I was contracting infections/viruses more frequently, which are more consuming when you are suffering from liver disease as well. This situation resulted in increased levels of antibiotics, time off work and decreased physical capability to function as a mother/homemaker & wife (especially when my partner isn't at home a lot due to work commitments and my family live 250 miles away). My performance in my career also drastically altered. I was turning up late as I'd not had a night's sleep and was leaving early as the day utterly wiped me out, which caused my weekly contracted hours to be down. Mistakes were being made and my general common sense approach had deteriorated. My usual attention to detail, my ability to provide solid business advice as well as to soak up new information were all suffering and it soon started to have an effect on my self-confidence and enthusiasm. Sadly and guiltily, during this time my child also endured as I was either not remembering her schedules or unable (as was ill or asleep) to cater for her as much as usual, which to me is a completely unacceptable state to be as a mother and something needed to be done about it. Finally, I notified my consultant about my experiences and after about 1-2 months of taking Rifaximin I noticed a significant change in my physical and mental state. It was like fragments of my typical self were steadily regaining and the overall irritability of the past few months were dispersing into the distant past. Gradually at last I was getting back my normal body clock and managing to get a full quota of sleep at the right time of the clock. My feeling of everything making sense had returned, my motivation increased and my home/work life balance soon got back on track as did the correct mother/daughter duties and relationship.	associated with hepatic encephalopathy (see FAD section 4.17). The Committee understood that the costs associated with constant care from family members and professional carers could not be built into the economic model, and factoring them in would improve the cost effectiveness of rifaximin (see FAD section 4.21).

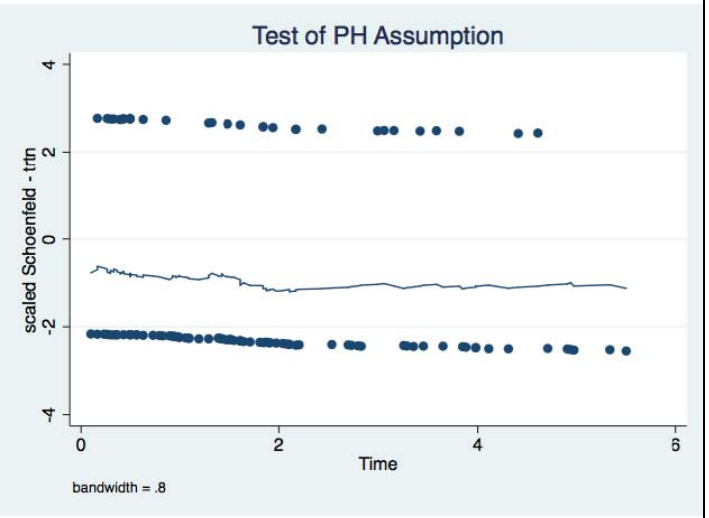
Consultee	Comment		Response
		I personally hope to have Rifaximin readily available for me on an indefinite term as I'm certain I wouldn't be at the place where I am now without it and could not even think nor tolerate being back as it was beforehand. November 2013 I am 56 years old. In 2008 I was admitted as an emergency patient losing massive quantities of blood due to oesophageal varices. After this I do not remember anything for several days. I believe I had a TIPS operation. After this everyone who visited me said I spoke complete gibberish. After about a week, I began to return to my usual self and was able to do crossword puzzles. I drove to the supermarket for essential provisions. The next day I began to realize things were not as good as I thought they should be. I could not operate the washing machine or the oven. As things got worse, I was unable to dress or feed myself. My elderly and disabled husband could only watch with rising panic. A GP visited, diagnosed encephalopathy and prescribed antibiotics. These worked after a while. The trouble was that these attacks would come on unpredictably and quickly. One day I was going to have lunch with my mother and in the course of an hour I lost the plot completely, drove to the wrong village and was found collapsed in a car park by some kind people who called an ambulance. Anyone in his right mind would have used a mobile to get help but I was not in my right mind and, to make matters worse, all these episodes are accompanied by a slurring of the voice leading to the assumption of drunkenness. I think I was hospitalized three times before I met Dr. [redacted] who prescribed Rifaximin. To me this has been a life changer - I can make appointments and be sure to be able to keep them. I can drive my car without fear for the safety of others. Now my husband is dead and I live alone. I have no-one to tell me that I am behaving	

Consultee	Comment				Response
			oddly or that my voice is slurred. Personally I do not realize when I have gone mad and because of that would not think of calling my GP. Rifaximin is my insurance against madness. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No. From my own personal experience, and the experience of our case studies, secondary costs and implications do not appear to have been taken into account in this appraisal. I appreciate that they may be difficult to quantify but they need to be accounted for somehow. Our feedback is that Rifaximin makes a difference to a lot of people. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? No. Again, based on the above testaments, not approving Rifaximin for use in the whole of the NHS would subject the lives of many people (with HE and caring for people with HE) to suffer the effects of HE needlessly. This technology can significantly improve the lives of many people, both affected by HE and caring for patients.		
Norgine	**No**	**ACD Section & Page Number**	**Relevant Text**	**Norgine's Comments**	Thank you for your comments.
	1.	Section 3.6 Page 8	The manufacturer also stated that there were no consistent differences between the rifaximin-α and placebo groups in change from baseline using the SF-36 and Epworth Sleepiness Scale.	• SF-36 and Epworth Sleepiness Scale were optional assessments and tertiary endpoints within the study (please see page 44 and 45 of the original submission) and measured changes from baseline to End of Study (EoS). • It is also worth considering that the study design with respect to the QoL endpoints may have been flawed, in that comparing baseline and EoS assessment scores may not be the most appropriate way to capture differences in QoL in this patient group. A time	The Committee understood that there are substantial challenges in capturing quality of life evidence in people with hepatic encephalopathy (see FAD section 4.17).

Consultee	Comment				Response
				weighted methodology appears to be more appropriate. • Please see Norgine Response to ACD Section 3.32, 4.3, 4.8 and 4.9 (below)	
	2.	Section 3.7 page 8-9	Section 3.7 Page 8-9	Norgine suggests the following text be added to the end of section 3.7 for clarity "This was primarily due to low patient numbers in these sub-groups."	The FAD notes that the company considered the lack of statistical significance was primarily because of small patient numbers (see section 3.7).
	3.	Section 3.19 Page 16	The manufacturer used the aggregated 6-month probability rather than individual probabilities of 61.29% for rifaximin-α and 49.32% for placebo on the basis that the rates of hepatic encephalopathy hospital admissions in the trial were not statistically significantly different between the 2 arms.	**Factual inaccuracy** Use of the word 'rates' is incorrect in this context. Rifaximin-α 550mg reduces the rate of hospitalisation due to HE compared to placebo. This was demonstrated clearly as a secondary endpoint of the pivotal study RFHE3001. Fewer patients in the rifaximin-α group (19/140) were hospitalised than the placebo group (36/159) - hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P = 0.01).	The FAD notes 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 (see section 3.24).
	4.	Section 3.20 Page 17	It then carried out regression analysis to derive the relationship between overall CLDQ scores from RFHE3001 and EQ-5D utility, which showed that 59% of the variation in the predicted EQ-5D utility was explained by the overall CLDQ score. The manufacturer also carried out a repeated measures analysis to quantify the relationship. The resulting parameter estimate for CLDQ was applied to the baseline CLDQ score, the increment in the CLDQ score for the rifaximin-α arm while in remission and the CLDQ scores for the overt state.	**Factual inaccuracy** The percentage variance explained (R-squared=0.59; or 59% as reported) refers to exploratory curve-estimation analysis which did not account for repeated observations within subjects. This analysis itself was not used to derive the relationship between CLDQ Overall score and EQ-5D utility but to determine the possible shape of any relationship in order to inform the choice of repeated measures model. As a linear curve was found to be a good fit to the relationship a General Linear Mixed Modelling approach to repeated measures analysis was selected using untransformed EQ-5D score as the dependent variable and untransformed CLDQ Overall score as a continuous covariate. In the resulting GLMM analysis, CLDQ was a highly	The description of the mapping approach has been amended in the FAD (see section 3.26).

Consultee	Comment				Response
				significant predictor (p<0.001) of EQ-5D, with little unexplained variance between observed utility score and those predicted by CLDQ (R-squared = 0.835). The strength of this association suggests that liver-related morbidity may explain the majority of differences in health-related utility in these subjects.	
	5.	Section 3.23 Page 19	The ERG identified a 6-month trial of rifaximin-α compared with neomycin reported by Miglio et al. (1997) which was not presented in the manufacturer's submission. The ERG acknowledged the manufacturer'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-α 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-α.	Use of neomycin in this indication is exceptional in UK clinical practice as evidenced by clinical expert opinion expressed at both committee meetings and in comments from consultees who did not agree that it would be a suitable comparator for this appraisal. Whilst the scope included neomycin this agent is rarely if ever used due to toxicity. Including this section in the guidance introduces inconsistency since in section 4.1 the Committee concluded that neomycin was not an appropriate comparator. ACD Section 4.1 *'The clinical specialists also 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 made it an unacceptable alternative. The Committee recognised the need for alternative treatment options in maintaining remission from episodes of hepatic encephalopathy and also concluded that neomycin was not an appropriate comparator for this appraisal'*	The Committee heard that neomycin is not used routinely in clinical practice, and concluded that neomycin was not an appropriate comparator (see FAD section 4.2). The description of the ERG's concerns reflects the views of the ERG and, in line with the NICE process, evidence that was part of the Committee's deliberations is presented in the FAD.
	6.	Section 3.24 Page 20	The ERG was concerned about the validity of this assumption, given that the treatment effect of rifaximin-α compared with placebo was not statistically significant in the subgroup with MELD scores of 19 to 24 (the more severe MELD score category in the trial). In addition, it noted that the study by Hassest et al. (2001), which	This was addressed at the last committee meeting where the clinical expert present validated this assumption as the primary reason that these subgroups didn't reach significance is due to the very small number of patients in these subgroups – the effect is still trending in the direction favouring rifaximin and is consistent with other subgroups. The concern of the ERG is not substantiated by the evidence. Figure 3 of the Bass et al clearly indicates that the mean effect favouring rifaximin in subgroup with the	The FAD acknowledges that the company emphasised the small patient numbers in this group (see section 3.7).

Consultee	Comment				Response
			was provided as evidence for the effectiveness of rifaximin-α in patients with MELD scores of 20 or more, was a poor quality descriptive study.	highest MELD scores is well within the confidence limits of the two more populous subgroup with lower MELD scores. That it does not achieve statistical significance is entirely to be expected from the very small numbers of patients available. The Hassest study, whilst being descriptive does provide some evidence of effect in patients with a high MELD score. It is also worthy of note that patients with MELD score ≥20 are more difficult to study for a number of reasons, including the ethical and practical constraints of assessing and studying patients with severe liver disease who are often close to the end of their life and thus may not complete the study . ***Please see below for Figure 3 from the Bass et al*** *[Norgine provided Figure 3 from Bass et al, N Engl J Med 362:1071–81; not reproduced here]*	
	7.	Section 3.26	The ERG stated that a 5-year time horizon was appropriate in the manufacturer's original model to capture the relevant costs and benefits, but stated that in the revised analysis a lifetime time horizon would have been appropriate given that approximately 52% of patients in the rifaximin-α arm and 45% of patients in the placebo arm were alive after 5 years.	A revision of the time horizon has been carried out in line with the committee's request. The last patient within the economic model dies at 42 years. This is Norgine's definition of life time horizon. Please see section 3 of Norgine Response to NICE TAC's Request for Further Analysis on Rifaximin-α 550mg.	Thank you for the additional evidence. The Committee concluded that the lifetime time horizon presented was appropriate (see FAD section 4.10).
	8.	Section 3.27 Page 21	The ERG reviewed the manufacturer's updated analysis and stated that it was unclear why the manufacturer used different time points to censor survival times when modelling	The schedule of assessments for RFHE3001 defines End of study (EoS) as 168 days ±2 days. Therefore, the revised presentation of regression coefficients based on 170 days censoring is more consistent with the design of the pivotal efficacy study (Bass et al). The treatment effect for rifaximin-α 550mg is identical whether 168 or 170 days	Thank you for the explanation. The Committee considered the revised analysis at day 170 to be more appropriate given that the clinical study report for

Consultee	Comment				Response
			breakthrough overt hepatic encephalopathy episodes; data censoring took place at day 168 in the manufacturer's original analysis and at day 170 in the updated analysis.	are used.	RFHE3001 reports data censoring at day 170 (see FAD section 4.11).
	9.	Section 3.27 Page 21-22	The ERG stated that the manufacturer should have carried out some validity tests to assess the assumption of a proportional treatment effect between rifaximin-α and placebo when fitting the parametric distributions to the trial data.	In order to test the proportional hazards assumption over the 6 month observation period of RFHE3001. A Cox proportional survival model was created so as to test the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that progressed to an event. The result of this analysis was also plotted in graphical form as shown. There was no significant correlation between treatment allocation and Schoenfeld residuals (p=0.1865); an observation supported by the horizontal plot of the same data. Therefore, no evidence was found for a violation of the proportional hazards assumption for treatment effect.  	Thank you for the additional information. This has been noted in the FAD (see FAD section 3.41).

Consultee	Comment				Response
				Time: Rank(t) rho chi2 df Prob>chi2 trtn -0.12372 1.75 1 0.1865 global test 1.75 1 0.1865 Examination of the subgroup analysis in the RFHE3001 provides evidence that the treatment effect is durable. Figure 3 shows that for subgroups defined by number of prior HE episodes (2 vs. >2 [max 9]) the HR for rifaximin is identical and highly statistically significant (p=0.002 and p=0.003 respectively). A near-identical pattern is also observed for subgroups defined by duration in covert / minimal HE state (*'remission'*) (≤90 days vs. >90 days).	
	10.	Section 3.28 Page 22	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.	Norgine recognises that a more detailed model would have been desirable to fully capture the complexity of disease progression. However, NICE's technical team had made it clear to Norgine that presentation of a new model structure would be unacceptable within the context of additional analysis (Addendum). Therefore, all revisions and supporting data have been presented consistent with the original model structure.	The Committee 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 revised model was an improvement on the original analysis and was appropriate for decision-making (see FAD section 4.9).
	11.	Section 3.28 Page 22	However, it stated that the manufacturer 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.	Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) have been calculated as suggested. The rank order of the candidate distributions presented in the Addendum is unchanged. An alternative parameterisation method for the Gompertz distribution consistent with the statistical application used to generate the parameter estimates (Stata) was ranked higher than the original Gompertz model (R) goodness of fit estimation presented in the Addendum.	Thank you for the additional information, it has been acknowledged in section 3.42 of the FAD.

Consultee	Comment				Response
				RFHE3001 C_1 to O_1 transition Model / Obs / ll(model) / AIC / BIC lognormal "cure" 299 -748.68 1499.36 1503.09 gompertz 299 -749.02 1500.05 1503.78 loglogistic 299 -752.93 1507.87 1511.60 weibull 299 -755.58 1513.16 1516.89 exponential 299 -758.56 1519.11 1522.84 gompertz "original" 299 -758.56 1519.11 1522.84 **RFHE3002new C_2 to O_2 transition** Model / Obs / ll(model) / AIC / BIC lognormal "cure" 102 -377.20 754.40 754.40 gompertz 102 -377.56 755.11 755.11 loglogistic 102 -377.80 755.60 755.60 weibull 102 -381.78 763.57 763.57 exponential 102 -388.57 777.14 777.14 gompertz "original" 102 -388.57 777.14 777.14 • Choice of distribution curve fitting the covert to first-observed BOHE (C_1 to O_1) has little impact on ICER (range £18,946 [weibull] to £20,829 [lognormal]). • Time constraints prevented exploration of all possible parametric modelling options. We do not believe the gamma distribution would significantly affect the ICER.	
	12.	Section 3.29 Page 23	The ERG stated that the manufacturer did not justify using different approaches to model mortality, that is, using survival analysis to model mortality in the remission states and using simple proportions to estimate the	The Addendum submitted by Norgine clearly states the methods used to calculate overt mortality (Addendum Sections 4.3.4.2 and 4.3.4.3, page 37) A simple proportion was calculated to estimate probability of death in overt state (O_1 & O_2) rather than survival analysis because the model fixes time in these states at 30.4 days. It is not reasonable to model survival over a	Thank you for the explanation. The description of the ERG's concerns reflects the views of the ERG and, in line with the NICE process, this is presented in the FAD. The Committee

Consultee	Comment				Response
			probability of death in the overt states. It also stated that the manufacturer did not also explain how it calculated the probability of death in the overt states.	period of one model cycle. Patients who did not die in these states were assumed to recover to a subsequent covert state (C_2). Probability of death in the overt state (O_1 and O_2 [all subsequent episodes pooled] respectively in RFHE3002) was calculated as: number of deaths within 31 days of HE onset/number of episodes. Standard errors of the probabilities have subsequently been calculated and applied in the PSA	considered both the ERG critique and all the evidence presented by the company and the Committee's conclusions are described in section 4.
	13.	Section 3.29 Page 23	It noted that the Kaplan-Meier curves were not provided for visual comparison of the different distributions used to model mortality in the remission state and stated that the manufacturer should have taken further steps to assess the goodness of fit of the distributions used to extrapolate mortality.	See Figure 7 below (from section 2.1.2 of Norgine Response to NICE TAC's Request for Further Analysis on Rifaximin-α 550mg). *[Norgine provided Figure 7 from the Norgine Response to NICE TAC's Request for Further Analysis on Rifaximin-α 550mg – not reproduced here]* **Figure 7. Fitted survival functions from RFHE3002 covert (C1) and subsequent covert (C2) states.**	Thank you for the additional information.
	14.	Section 3.29 Page 23	The ERG also highlighted the inconsistency in the use of RFHE3002 data in the model, in which data for all patients in RFHE3002 were used to model mortality, whereas only data for new patients in RFHE3002 were included in the modelling of subsequent episodes.	The reason for use of different subsets for different inputs was clearly explained in the Addendum. (Addendum Sections 2.2.3 [Subsequent BOHE Episodes] and 4.3.2 [Mortality]) Whilst there were sufficient subsequent HE episodes in RFHE3002 new patients to calculate parametric survival models, there were insufficient deaths in this subgroup to inform survival modelling. Covert mortality: new patients, 11 deaths; rollover patients, 6 deaths; crossover patients, 6 deaths. Subsequent covert mortality: new patients, 8 deaths; rollover patients, 4 deaths; crossover patients, 7 deaths. The overall modelled mortality is a very close fit to clinically observed mortality in patients surviving a median of 11 months following first-ever HE *[Norgine provided Figure 23 from the Addendum to*	Thank you for the explanation. The description of the ERG's concerns reflects the views of the ERG and, in line with the NICE process, this is presented in the FAD.

Consultee	Comment				Response
				Norgine NICE STA Submission on Rifaximin-α 550mg: Further Analyses in Response to Technology Appraisal Committee's Critique of the Economic Case – not reproduced here] Key to figure: grey line, CPRD HE patients from 11 months after 1st HE code, censored by liver transplant; black line, 3002 mortality, all patients ; green line, modelled lactulose; yellow line, modelled rifaximin. Please see Figure 3 of the Addendum – no statistically significant difference between cross-overs, roll-overs and new patients in transition to first observed HE. Therefore modelling covert mortality with combined RFHE3002 data was justified. *[Norgine provided Figure 3 from the Addendum to Norgine NICE STA Submission on Rifaximin-α 550mg: Further Analyses in Response to Technology Appraisal Committee's Critique of the Economic Case – not reproduced here]* **Figure 1. Unadjusted KM plots of time to first BOHE event stratified by OLT subgroup (red, 3001 placebo crossover; green, 3002 new; blue, 3001 rifaximin rollover)**	
	15.	3.30	The ERG compared mortality from RFHE3001, RFHE3002, the CPRD data and the revised model. It noted that the model over-estimated mortality for the placebo arm at 6 months (10%) compared with RFHE3001 (7%), whereas mortality estimated for the rifaximin-α arm at 6 months was similar to that in RFHE3001 (7%)	One would not expect to see differences in mortality at 6 months as this was not a specified end point of RFHE3001. In addition, the study was not powered to detect mortality differences over such a short time period. Norgine has further explored the data relating to mortality in this patient population and presented a sensitivity analysis as requested by the Committee (Please see Section 2 of Norgine Response to Committee's Requests), which illustrates that the cost-effectiveness of rifaximin-α is no longer primarily driven by mortality.	Thank you for the additional evidence. The Committee considered the results of the company's economic model submitted in response to the second consultation and the scenario analyses exploring alternative mortality assumptions (see FAD section 4.19).
	16.	3.30	The ERG stated that clinical opinion indicated that, although the survival benefit predicted was	Modelled mortality is lower than typically seen when measured from first HE episode (e.g. Bustamante, CPRD analysis) precisely because the modelled population is	Thank you for your comments. The Committee considered in detail the

Consultee	Comment				Response
			reasonable, the overall mortality seemed low for patients in both arms of the model It also noted that 2-year mortality for the rifaximin-α arm was similar to that observed in RFHE3002 and that 5-year mortality estimated from the model showed an incremental survival benefit of 8% for rifaximin-α compared with placebo	that recruited to the RFHE3001 and RFHE3002 studies whose median time from first HE episode was 11 months, placing them at a much lower hazard of death than would be expected from first HE episode. The comparison of observed overall mortality from RFHE3002 with that of CPRD patients left censored at 11months (median time from first HE to recruitment into the OLE study), as illustrate in the previous figure shows that the former is representative of UK clinical practice and therefore an appropriate data source for modelling mortality in this patient population.	possible mortality benefit associated with rifaximin. It noted that the mortality predicted by the October 2013 model was similar to that in the Clinical Practice Research Datalink (CPRD), and in RFHE3001 and RFHE3002 (see FAD section 4.19).
	17.	Section 3.30 Page 23	… 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).	It is not unexpected that only 1 liver transplant was reported in the pivotal study since the following was an exclusion criterion for the study *'Subject was expected to receive a liver transplant within 1 month of screening'*.	Comment noted.
	18.	Section 3.31 Page 24	However, it stated that clinical opinion did not support the use of an aggregated probability for the rifaximin-α and placebo arms, even though the manufacturer 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	This makes minimal difference to the ICER. Norgine's base case with a life time horizon used an aggregate probability of HE hospitalisation of 52.88% for which the ICER was £17,826/QALY. For a sensitivity analysis where probability HE hospitalisation was split by observed data for treatment arms in RFHE3001 61.3% vs.49.3%, the ICER was £18,130/QALY.	The Committee noted this approach and considered it to be selective. It considered that the individual rates would have been more appropriate, although it noted that the impact on the incremental cost effectiveness ratio (ICER) was minimal (see FAD section 4.12).
	19.	Section 3.32 Page 24	The ERG stated that it was unclear why the manufacturer used the EQ-5D utility values estimated from the condition-specific CLDQ in the model given	In Norgine's view deriving Utility from the time weighted average CLDQ is the most appropriate methodology and thus should form the base case for cost-effectiveness analysis for the following reasons:	The Committee considered in detail the approaches to modelling utility. It expressed several concerns about the

Consultee	Comment				Response
			that it was possible to incorporate values directly from mapping the SF-36 utilities onto the EQ-5D.	1. Domains of SF-36 have a much wider variance than CLDQ domains (CSR RFHE3001) suggesting it is a less precise instrument for measuring QoL in this patient population with underlying cognitive impairment 2. CLDQ is a disease specific (liver) QOL instrument and SF-36 is a generic QOL instrument. Observed differences in utility derived from disease specific and generic instruments are not unusual across therapy areas and in the pivotal study (CSR RFHE3001) 3. SF-36 was an optional instrument in the scheduled assessments whereas CLDQ was a required assessment (in USA and Canada). Therefore, we it would be expected that this would increase the likelihood of non-random missing data in the SF-36 dataset compared to CLDQ. This indeed was the case: ▪ Proportion of patients not completing the questionnaire were ❖ [redacted] ▪ Proportion of missing values ❖ [redacted] 4. Finally, the use of the SF-36 tool has been shown to be of poor quality in patients with cognitive impairment and therefore is a sub-optimal measure of QoL in patients with Hepatic Encephalopathy, who by the very nature of their condition, have significant neurocognitive impairment, throughout the covert / minimal HE ('remission') and overt states. The above limitations of the SF-36 would not, however, preclude a mapping analysis between CLDQ and Utility derived from SF-36. Mapping approaches to utility derivation are reasonable as long as the uncertainty associated with the estimate are incorporated appropriately into the modelling exercise[3]	company's approach of using both SF-36 and CLDQ to derive utility scores. The Committee 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. 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. It concluded that the most appropriate approach for deriving the utility scores was the analysis based on SF-36 data only (see FAD section 4.14).

Consultee	Comment				Response
				(NICE DSU Technical Support Document 10). The two sources of uncertainty inherent in the two-stage mapping of CLDQ to utility have been incorporated in the PSA: a) the 95% CI of the CLDQ Overall score LS mean benefit for rifaximin-α in the covert / minimal HE state (*'remission'*) and b) the 95% CI of the parameter estimate from the repeated measures regression. **Reference:** 1. Salix Pharmaceuticals Inc. Clinical Study Report. A Multi-Center , Randomized , Double-Blind , Placebo Controlled Trial to Evaluate the Efficacy , Safety and Tolerability of Rifaximin 550 mg BID for 6 Months in Preventing Hepatic Encephalopathy (RFHE3001). Morrisville, NC, 2009. 2. Sanyal A, Younossi ZM, Bass NM, *et al.* Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61. 3. Longworth, L., Rowen, D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011. Available from http://www.nicedsu.org.uk 4. Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J. General health status measures for people with cognitive impairment: learning disability and acquired brain injury. Health Technol Assess 2001;5(6).	
	20.	Section 3.32 Page 24-25	It was concerned that the estimated quality-of-life increment with rifaximin-α compared with placebo in the remission state was in contrast to the	In the first ACD, the Committee questioned why Norgine had not used the QoL data collected during the RFHE3001 study in the original submission. In response to this, Norgine re-examined these data in detail using the methodology described elsewhere and noted significant	Comment noted. The FAD notes that the company presented evidence based on re-examination of quality-of-

Consultee	Comment				Response
			manufacturer's original analysis in which the impact on quality of life was linked to movement between the overt and remission health states only.	changes in time-weighted utility between the rifaximin and placebo arms for patients in the covert state and applied this in the model.	life data from RFHE3001 (section 3.26) The Committee concluded 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 increment (see FAD section 4.16).
	21.	Section 3.32 Page 25	The ERG stated that there was uncertainty in the validity of the utility increment estimated for the rifaximin-α arm given that the manufacturer appeared to have measured the value in centimetres directly from the study by Sanyal et.al rather than using the actual published value of difference in least square means.	Norgine did not have access to the original data files of the Sanyal post hoc analysis, nor were the numbers underpinning the Figures published, therefore our only option (within the time available to submit the revised analysis) was to obtain the data by measurement. As digital measurement (using DigitizeIt software) was accurate to 0.1mm we do not believe this introduced any significant uncertainty into the model.	Comment noted.
	22.	Section 3.32 Page 25	It also highlighted that applying the increment to the remission state 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.	As the data from Sanyal et al only considered those values observed in the covert state ('*remission*'), Norgine considers that the decision to incorporate the increment into the covert states only was a reasonable one. **Reference**: Sanyal A, Younossi ZM, Bass NM, *et al.* Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61.	Comment noted.
	23.	Section 3.32 Page 25	The ERG stated that the utility values used in the model were a key driver of the results given that excluding the utility increment from the rifaximin-α arm of the remission state increased the	Norgine recognise that utility is a key driver of cost-effectiveness in the model. Clinical opinion unanimously supports a clinically meaningful improvement in quality of life associated with rifaximin-α therapy. Therefore, the scenario modelled by the ERG is not clinically plausible.	The Committee concluded that rifaximin could be associated with a utility increment in the remission states and that there are substantial challenges in

Consultee	Comment				Response
			ICER to £59,421 per QALY gained.		identifying the most plausible value for this increment (see FAD section 4.16).
	24.	Section 3.33 Page 25	However, it noted that the cost of outpatient attendance for non-hospitalised hepatic encephalopathy events used in the updated analysis (£176.27) was different from the cost of £110.68 used in the original analysis	The cost in the original submission was incorrectly specified from the tariff for 'Clinical Haematology' (Service Code 303). This was corrected in the Addendum to the tariff for 'Hepatology' (Service Code 306).	Thank you for the clarification. The costs described in the FAD (section 3.30) reflect the costs included in the economic model in the December 2013 and November 2014 submissions.
	25.	Section 4.2 Page 27	The Committee noted that patients with more severe liver disease (Model End Stage Liver Disease [MELD] score of 25 or more) were excluded from the trial, but that the manufacturer had suggested that 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-α in the subgroup of patients 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 patients in RFHE3001. However, the Committee heard from the clinical specialists that, in practice, patients with a MELD score greater than 24 have a poor prognosis and are often hospitalised awaiting liver transplant. The clinical specialists stated that rifaximin-α would not	Norgine would like to clarify that non significance was due to small 'n' numbers of patients (26 out of 299). The data did, however, show a trend towards significance. (text from Norgine's Response to the 1st ACD) For clarity, patients with MELD score ≥25 were excluded from RFHE3001 for a number of reasons, including the ethical and practical constraints of assessing and studying patients with severe liver disease who are often close to the end of their life. Extensive consultation with clinical experts revealed that patients with MELD Score >19 are treated with rifaximin-α in clinical practice. However, the treatment goals are focused on improvement in QoL / optimisation of the patients clinical condition to make them candidates for liver transplantation. The concern of the ERG is not substantiated by the evidence. Figure 3 of the Bass study clearly indicates that the mean effect favouring rifaximin in subgroup with the highest MELD scores is well within the confidence limits of the two more populous subgroup with lower MELD scores. That it does not achieve statistical significance, is entirely to be expected from the very small numbers of patients available. The Hassest study, whilst being descriptive does provide	The FAD states that the Committee recognised that this subgroup comprised only 26 of the 299 patients in RFHE3001 (see section 4.3)

Consultee	Comment				Response
			generally be prescribed for these patients because it was unlikely to provide any meaningful benefit.	evidence of effect in patients with a high MELD score.	
	26.	Section 4.3 Page 28 (Also Summary of Appraisal Committee's key conclusions) Page 40 - 45	However, the improvements in asterixis score and venous ammonia levels were not statistically significant, and the difference in changes in CLDQ fatigue scores, SF-36 scores and Epworth Sleepiness scale scores between the rifaximin-α arm and placebo arm was minimal.	To clarify, these were tertiary endpoints (ESS and SF-36) for which the trial was never powered. Also, patients who had an episode of BOHE exited the trial (RFHE3001) as per the study protocol. Therefore, patients for whom QoL data were available at end of study were all in the covert (minimal HE) state as they were at the beginning of the study. Consequently, it cannot be expected (a priori) that statistically significant unadjusted differences in QoL would be detectable between baseline and last measurement. It is important to note that, because of altered mental and neuromotor status, it was not possible for subjects to complete the CLDQ, SF-36 and other QoL assessments during an overt HE breakthrough episode. Thus some CLDQ assessments must have occurred as patients were entering an overt episode (which would only have been evident after diagnosis of the episode). Therefore, as mental status was closer to baseline levels at the time of end of treatment assessments, QoL results may have been similar to baseline levels for subjects who had breakthrough overt HE episodes. The planned statistical analysis did not take into account that patients at the end of the study would be those who never experienced a BOHE and was flawed in that respect. Post hoc analysis of CLDQ data (Sanyal et al 2011) showed significant improvement for rifaximin over placebo in all domains of disease-specific QoL and in 27 of 29 individual item responses. As we have previously stated, QoL is extremely difficult to measure in these patients. For the following reasons: 1. Cognitive impairment whereas patients believe	Comments noted. The Committee understood that there are substantial challenges in capturing quality of life evidence in people with hepatic encephalopathy (see FAD section 4.17).

Consultee	Comment				Response
				they are perfectly normal 2. Generic measures e.g. SF-36 3. Time weighted averages are the most useful way of capturing Please also see Response to: • ACD Section 3.32; regarding CLDQ and SF-36 scores • ACD Section 3.6 **Reference:** Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. Alimentary Pharmacology & Therapeutics 2011; 34: 853–61.	
	27.	Section 4.5 Page 30	The Committee considered the manufacturer's economic model and the ERG's critique of the model. It accepted the exclusion of neomycin from the analysis because it was not routinely used in clinical practice. The Committee noted that after consultation, the manufacturer amended the way it estimated the risk of subsequent episodes and that the revised 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, that is, subsequent remission state and subsequent overt state; thereby ignoring the number of episodes. However, it noted that including more health states for subsequent episodes	As stated above, whilst Norgine recognises that a more detailed model would have been desirable to fully capture the complexity of disease progression, due to the constraints of what type of analysis would be accepted as additional analysis it was not possible to fully explore separating out subsequent BOHEs, whilst remaining consistent with the original model structure. (See Norgine Response to ACD Section 3.28 …page 22)	The Committee 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 revised model was an improvement on the original analysis and was appropriate for decision-making (see FAD section 4.9).

Consultee	Comment				Response
			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, the revised model was an improvement on that used in the manufacturer's original analysis, which oversimplified the nature and course of the disease.		
	28.	Section 4.6 Page 31	It noted that the ERG had conducted an exploratory analysis with a lifetime time horizon where all patients died after 35 years. However, it heard from the clinical specialist that people with hepatic encephalopathy would not survive for up to 35 years because of their underlying liver cirrhosis. The clinical specialist stated that life expectancy usually ranged between 5 and 15 years depending on disease severity, stating that it was even lower for people with severe disease who had not had a liver transplant. The Committee noted that a time horizon of 35 years did not imply that all patients survived for 35 years. It considered that the prolonged survival of 35 years 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. The	It is unclear how the ERG conducted their exploratory analysis of a 35 year life time horizon. Also, this is in contradiction to ACD Section 3.26 which states the ERG used a life time horizon of 40yrs. Norgine has carried out further analysis using a life time horizon, as per the committee's request and this resulted in a 42 year time horizon by which time the last patient within the economic model is dead. Please see section 3 of Norgine Response to NICE TAC's Request for Further Analysis on Rifaximin-α 550mg	Thank you for the additional evidence. The text in the FAD has been drafted to describe the ERG's exploratory analysis more clearly (see sections 3.40 and 4.10). The Committee concluded that the lifetime time horizon was appropriate (see section 4.10).

Consultee	Comment				Response
			Committee concluded that the manufacturer's choice of a 5-year time horizon was not in line with the NICE reference case and that a lifetime time horizon would be more appropriate to capture all relevant costs and benefits. It recommended that further analyses using a lifetime time horizon be requested.		
	29.	Section 4.8 Page 33	First, the Committee was unsure why the manufacturer had not presented results based on mapping SF-36 data collected from RFHE3001 directly to EQ-5D. The Committee considered that incorporating further modelling steps after the mapping exercise to quantify the relationship with CLDQ scores unnecessarily introduced further uncertainties in the analysis.	The high variance in SF-36 scores compared to CLDQ scores indicates that SF-36 is insufficiently sensitive to capture the QoL benefits of rifaximin treatment. In Norgine's view deriving Utility from the time weighted average CLDQ is the most appropriate methodology and thus should form the base case for cost-effectiveness analysis for the following reasons: 1. Domains of SF-36 have a much wider variance than CLDQ domains (CSR RFHE3001) suggesting it is a less precise instrument for measuring QoL in this patient population with underlying cognitive impairment 2. CLDQ is a disease specific (liver) QOL instrument and SF-36 is a generic QOL instrument. Observed differences in utility derived from disease specific and generic instruments are not unusual across therapy areas and in the pivotal study (CSR RFHE3001) 3. SF-36 was an optional instrument in the scheduled assessments whereas CLDQ was a required assessment (in USA and Canada). Therefore, we it would be expected that this would increase the likelihood of non-random missing data in the SF-36 dataset compared to CLDQ. This indeed was the case: ▪ Proportion of patients not completing the questionnaire were ❖ [redacted]	The Committee considered in detail the approaches to modelling utility. It expressed several concerns about the company's approach of using both SF-36 and CLDQ to derive utility scores. The Committee 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. 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. It concluded that the most appropriate approach for deriving the utility scores was the analysis based on SF-36 data only (see FAD section 4.14).

Consultee	Comment				Response
				[redacted] ▪ Proportion of missing values ❖ [redacted] 4. Finally, the use of the SF-36 tool has been shown to be of poor quality in patients with cognitive impairment and therefore is a sub-optimal measure of QoL in patients with Hepatic Encephalopathy, who by the very nature of their condition, have significant neurocognitive impairment, throughout the covert / minimal HE ('remission') and overt states. The above limitations of the SF-36 would not, however, preclude a mapping analysis between CLDQ and Utility derived from SF-36. Mapping approaches to utility derivation are reasonable as long as the uncertainty associated with the estimate are incorporated appropriately into the modelling exercise[3] (NICE DSU Technical Support Document 10). The two sources of uncertainty inherent in the two-stage mapping of CLDQ to utility have been incorporated in the PSA: a) the 95% CI of the CLDQ Overall score LS mean benefit for rifaximin-α in the covert / minimal HE state (*'remission'*) and b) the 95% CI of the parameter estimate from the repeated measures regression. **Reference:** 1. Salix Pharmaceuticals Inc. Clinical Study Report. A Multi-Center , Randomized , Double-Blind , Placebo Controlled Trial to Evaluate the Efficacy , Safety and Tolerability of Rifaximin 550 mg BID for 6 Months in Preventing Hepatic Encephalopathy (RFHE3001). Morrisville, NC, 2009. 2. Sanyal A, Younossi ZM, Bass NM, *et al.*	

Consultee	Comment				Response
				Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61. 3. Longworth, L., Rowen, D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011. Available from http://www.nicedsu.org.uk Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J. General health status measures for people with cognitive impairment: learning disability and acquired brain injury. Health Technol Assess 2001;5(6).	
	30.	Section 4.9 Page 34	The Committee also expressed concern regarding the face validity of the utilities used in the model. It noted that the difference between the remission and overt state utility values was less than the benefit assumed for rifaximin-α compared with placebo for the remission state.	The intention with the model revisions was to use input assumptions substantiated with available data. Given that a small number of CLDQ observations from RFHE3001 had been made in the overt state, a health state utility was estimated from this. It is important to highlight that as a patient enters an overt episode, their ability to adequately complete a QoL questionnaire becomes progressively impaired to the point where this becomes impossible once the patient has fully entered the overt state. The above CLDQ assessments must, therefore, have occurred as patients were entering an overt episode (which would only have been evident after diagnosis of the episode). For this reason, the assessment would not capture the full disutility associated with the overt HE episode. Thus, the values presented may well be an underestimation and has the effect of making the model conservative.	The Committee's considerations of the utility scores are described in sections 4.14 to 4.17 of the FAD. The Committee considered that although a utility benefit with rifaximin was plausible, a utility benefit of 0.106 in the remission state was not reliable. It concluded that the most appropriate utility increment for decision-making was 0.032.
	31.	Section 4.9 Page 35 (Also Summar	Given the concerns around methodology and the inconsistencies identified in the results available, the Committee considered that the utility	This analysis has been carried out in line with the committee's request. Please see Section 4 of Norgine Response to Committee's Requests. With respect to uncertainties surrounding use of the CLDQ EQ-5D mapping function, the requested PSA for	Comments noted. The Committee noted that the utility estimates used in the December 2013 and November 2014 models were

Consultee	Comment				Response
		y of Appraisal Committee's key conclusions) Page 40 - 45	estimates driving the model were not robust. The Committee concluded that it would be more appropriate to use utility values estimated by mapping SF-36 data from the entire RFHE3001 population directly to EQ-5D and it recommended that further analyses incorporating this data be requested.	the Norgine Basecase incorporates the uncertainty of both the LS mean incremental difference in CLDQ Overall score favouring rifaximin-α (Sanyal et al)[1] and that of the parameter estimate relating CLDQ to EQ-5D of the repeated measures modelling. This is line with NICE's recommendation (NICE DSU Technical Support Document 10)[2]. **Reference:** 1. Sanyal A, Younossi ZM, Bass NM, *et al.* Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 2011; **34**: 853–61. 2. Longworth, L., Rowen, D. NICE DSU Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011. Available from http://www.nicedsu.org.uk	improvements on those used in the original and October 2013 models.
	32.	Section 4.10 Page 35	It also noted that length of stay was assumed to be 5 days in the model, whereas data from Hospital Episode Statistics for encephalopathy admissions suggests mean stays of around 17 days. The clinical specialist stated that an assumption of 5 days was reasonable. The Committee considered it would have been useful for this information to have been collected in the trial so that differences in length of stay could have been appropriately captured in the model.	There is no HE specific ICD or HRG code. All available codes are surrogates as shown below (HES 2012): 1) For ICD-10 G93.4 'Encephalopathy, unspecified' mean LoS = 17 days, median LoS = 8 days 2) For ICD-10 K72.9 'Failure, hepatic' mean LoS = 12.4 days, median LoS = 7 days 3) For ICD-10 K70.4 'Alcoholic hepatic failure' mean LoS = 13.6 days, median LoS = 8 days 4) Weighted averages for HRGs GC01 & GC15, mean LoS = 13.5, median LoS = 8.7 It is worthy of note that the Norgine assumption of 5 days is conservative and based on clinical expert opinion. **Reference:** HES Summary Data 2012	Comment noted. The Committee discussed in detail the effect of rifaximin on hospital admissions, and understood that the data from Hospital Episode Statistics was based on surrogate disease codes (see section 4.12 of the FAD).
	33.	Section 4.11 Page 36	However, the Committee was concerned that the model predicted a difference of 3.6% in the risk of mortality with rifaximin-	One would not expect to see differences in mortality at 6 months as this was not a specified end point of RFHE3001. In addition, the study was not powered to detect mortality differences over such a short time period.	Thank you for the additional evidence. The Committee considered the results of the company's economic model

Consultee	Comment				Response
			α compared with placebo during the first 6 months of the model and a difference of up to 8% over the 5-year time horizon. It noted that no differences in mortality between rifaximin-α and placebo were observed in RFHE3001	Norgine has further explored the data relating to mortality in this patient population and presented a sensitivity analysis as requested by the Committee (Please see Section 2 of Norgine Response to Committee's Requests), which illustrates that the cost-effectiveness of rifaximin-α is no longer primarily driven by mortality. Please see response to ACD section 3.30 and 4.11(below)	submitted in response to the second consultation and the scenario analyses exploring alternative mortality assumptions (see FAD section 4.19).
	34.	Section 4.11 Page 37	The Committee was not persuaded that these data provided robust evidence for a differential mortality benefit for rifaximin-α for preventing recurrence of overt hepatic encephalopathy.	The evidence for elevated mortality immediately following HE is well documented [Shawcross et al]. As rifaximin-α is effective in preventing HE episodes the case for an indirect mortality benefit is entirely plausible and supported by clinical experts. Please also see response to ACD Section 4.12 (below) **Reference:** Shawcross DL, Sharifi Y, Canavan JB, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. Journal of hepatology 2011; 54: 640–9.	The Committee concluded that although a mortality benefit had not been seen in the RFHE3001 study, 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 concluded that the magnitude of the effect is uncertain (see FAD section 4.18).
	35.	Section 4.12 Page 37	The Committee expressed concern that the model predicted an increasing differential mortality benefit for rifaximin-α when clinical experience indicates decreasing clinical efficacy over time in preventing overt hepatic encephalopathy episodes. The clinical specialist stated that it was plausible that rifaximin- α could have an impact on mortality and the modelled differential seemed reasonable but acknowledged that, with disease progression, the effect in preventing overt hepatic encephalopathy episodes would	The model inputs for mortality in the four health states C_1, C_2, O_1 and O_2, are the same for the rifaximin-α and lactulose cohorts. No explicit differential mortality benefit is included in the model. Differences in mortality in both the covert and overt states derive from the reduction in episodes of overt HE provided by rifaximin-α treatment. In the covert state, mortality inputs were obtained by using the best-fit parametric proportional hazards survival models from RFHE3002. In the C_1 state this was found to a log normal distribution and Weibull for C_2. Mortality risk was found to be higher in the C_2 state than in C_1. An increasing risk of mortality after each HE event is clinically plausible as such an event marks a deterioration in underlying liver disease status and will have had systemic	Thank you for your comments and for the additional evidence. The Committee recognised that the modelled mortality benefit came from avoiding overt episodes rather than an explicit survival benefit applied to the rifaximin arm. The Committee concluded that although a mortality benefit had not been seen in the RFHE3001 study, it was willing to accept that an initial mortality benefit with rifaximin

Consultee	Comment				Response
			decrease and that there would be additional causes of death, independent of hepatic encephalopathy, including renal failure, sepsis and bleeding from oesophageal varices.	effects from which the patient may not fully recover. This has been clearly established for cognitive function where patients do not fully return to pre-episode levels [1]. In the overt state mortality risk was calculated from the 30-day mortality following O_1 and O_2 events, 11% and 8% respectively. This acute elevation in the risk of death following breakthrough overt HE is well established (Bustamante et al., 1999; Shawcross et al., 2011). As these risks were applied to both cohorts in the model it is clear that no direct differential mortality was assumed. Differences in mortality arise from the reduction in HE episodes in the rifaximin-α group by two mechanisms: 1) avoidance of the acute mortality associated with O_1 and O_2 and; 2) longer retention in the C_1 state with exposure to a lower hazard of death than equivalent cases who transition to the C_2 state having recovered from O_1. Both mechanisms contributing to accrued mortality benefit for rifaximin-α are clinically plausible. In the model, prior to the first HE episode, both cohorts have the same risk of dying, the rate derived from the log normal distribution derived from RFHE3002. During the first overt HE episode both cohorts have an 11% risk of death. In patients who survive the first and subsequent episodes the mortality risk for both cohorts is derived from the Weibull distribution obtained from RFHE3002. The mortality risk during the second and any further overt episodes is 8% for both cohorts. Norgine sought additional clarification from NICE's Technical Team on how to address the committee's request on '*a clinically plausible diminishing mortality benefit with rifaximin-α over time'* in a rational and clinically plausible manner. It was felt that there may be a potential misunderstanding of the way that mortality is derived in the model that may have led to this request. It	resulting from a reduction in overt hepatic encephalopathy episodes was plausible. However, it concluded that the magnitude of the effect is uncertain (see FAD sections 4.18 and 4.19).
	36.	Section 4.12 Page 38	'The Committee also noted that the ERG's exploratory analysis indicated a modelled mortality benefit for rifaximin-α in the remission state that was independent of the effect in preventing episodes of overt hepatic encephalopathy. The Committee noted from the ERG's exploratory analyses that excluding a differential mortality benefit with rifaximin-α from the remission state increased the ICER to £22,700 per QALY gained and to £30,200 per QALY gained when mortality benefit was excluded from both health states'.		
	37.	Section 4.13 Page 39	4.13 "The Committee was concerned about the incremental benefit with rifaximin-α in the remission state and the increasing mortality benefit with disease progression."		

Consultee	Comment				Response
				was felt that Norgine's clarification on this may help address the committee's concerns. Norgine believes the Committee's perception of the incremental benefit with rifaximin-α in the covert / minimal HE state (*'remission'*) and the increasing mortality benefit with disease progression, is an artefact of taking a short term view of the model outputs. Taking a longer term view, consistent with the Committee's request to use a life time horizon, revised model outputs demonstrating that there is a clinically plausible diminishing mortality benefit within the previously submitted model are presented in figure 6 (Section 2.1.2) of Norgine Response to Committee's Requests. 1. Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology. 2010;138:2332-2340. 2. Bustamante, J., Rimola, a, Ventura, P. J., Navasa, M., Cirera, I., Reggiardo, V., & Rodés, J. (1999). Prognostic significance of hepatic encephalopathy in patients with cirrhosis. Journal of hepatology, 30(5), 890–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20508990 3. Shawcross, D. L., Sharifi, Y., Canavan, J. B., Yeoman, A. D., Abeles, R. D., Taylor, N. J., … Wendon, J. A. (2011). Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. Journal of hepatology, 54(4), 640–9. doi:10.1016/j.jhep.2010.07.045	
	38.	Section 4.13 Page 39	The Committee was also concerned that the manufacturer did not report a probabilistic ICER that would take account of all the uncertainties in the model parameters simultaneously.	The probabilistic Sensitivity Analysis has been carried out as per the committee's request with the following results: Probabilistic ICER: £29,551/QALY; probability of cost-effectiveness at WTP £30K, 42%. Please see Section 4 of Norgine Response to Committee's Requests.	Thank you for the additional evidence. The Committee considered the results of the probabilistic sensitivity analysis in its consideration of the company's December 2013 submission.

Consultee	Comment				Response
	Norgine Clarification on Factual Inaccuracies in the ACD on Rifaximin-α 550mg issued Nov 2013				
	Page No	**Section of ACD**	**Relevant Text**	**Norgine Clarification**	
	Page 12-13	ACD Section 3.14	In the original submission, a Markov cohort model consisting of 3 states (remission, overt and dead) was developed to reflect the clinical pathway of hepatic encephalopathy.	The model in the original submission always had two phases held within its structure. An initial phase describing patients moving from an covert C_1 state to an Overt O_1 state and then subsequently a second phase of patients that experience a second covert state C_2 and a subsequent second Overt event. Norgine accept that it was not well described in the first submission. The secretariat indicated that there should not be substantial structural change to the model presented at the second stage of the process. Norgine thus did not modify this two phase structure in its second submission. The company did change the data inputs and mathematical extrapolations to better fit clinical expert opinion and feedback from the appraisal committee.	Thank you for the clarification. The FAD describes that the model consisted of 5 states (see section 3.17).
		Section 3.19 Page 16	The manufacturer used the aggregated 6-month probability rather than individual probabilities of 61.29% for rifaximin-α and 49.32% for placebo on the basis that <u>the rates of hepatic encephalopathy hospital admissions in the trial were not statistically significantly different between the 2 arms.</u>	Use of the word 'rates' is incorrect in this context. Rifaximin-α 550mg reduces the rate of hospitalisation due to HE compared to placebo. This was demonstrated clearly as a secondary endpoint of the pivotal study RFHE3001. Fewer patients in the rifaximin-α group (19/140) were hospitalised than the placebo group (36/159) - hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P = 0.01).	Thank you for the clarification. The FAD notes 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 (see section 3.24).
		Section 3.19 Page 16	However, in the revised analysis, the manufacturer applied the aggregated 6-month probability of 52.88% to both arms of the model. <u>The manufacturer used the aggregated 6-month probability rather than individual probabilities of 61.29% for rifaximin-α and 49.32% for</u>	In line with the statement above, the probability of a patient who had experienced an episode of being hospitalised was not statistically significantly different between study arms (of 61.29% for rifaximin-αand 49.32% for placebo p=0.263). Hence the use of aggregated probability (52.88%).	Thank you for the clarification. The FAD notes 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 (see section 3.24).

Consultee	Comment				Response
			placebo on the basis that the rates of hepatic encephalopathy hospital admissions in the trial were not statistically significantly different between the 2 arms.		
	Page 18	Section 3.21	No administration costs were included in the model because rifaximin-α and lactulose are taken orally; therefore the total costs of treatment per month were £288.34 for the rifaximin-α group compared with £7.31 for the placebo group. The manufacturer estimated a total monthly cost of £36.89 for an outpatient visit in the remission state and £359.73 compared with £292.96 for the overt state (outpatient visit plus hospital admission for 5 days) for the rifaximin-α and placebo groups respectively.	Comment – are these costs correct for the overt state? All other comments are on pdf Descriptive of: • Covert health state cost: applicable equally to both arms – £58.76 monthly (quarterly Hepatology outpatient attendance) • Overt Health state cost: applicable equally to both arms - £1040.77 ([5 days inpatient hepatology admission x 52% risk hospitalisation] + outpatient attendance. • Drug cost: rifaximin - £289.95 monthly (£281.80 rifaximin, £8.15 lactulose); standard of care - £9.09 monthly (lactulose) The original model had incorrectly specified the Hepatology outpatient attendance tariff (resulting in an underestimate).	Thank you for the clarification. The costs described in the FAD reflect the costs included in the economic model (see section 3.30).
	Page 27	ACD Section 4.2	However, the Committee noted that mortality was not reported because the data were not considered mature enough to assess mortality.	Mortality was reported in RFHE3001 but as the study was of only 6 months duration the data were not considered mature enough to inform the economic model.	Thank you for the clarification. The FAD notes that mortality was not reported because the data were not considered mature enough to assess the effect of rifaximin on mortality (see section 4.3).

Consultee	Comment				Response
	Page 28	Section 4.3 (Summary of Appraisal Committee's key conclusions Page 40 - 45)	However, the improvements in asterixis score and venous ammonia levels were not statistically significant, and the difference in changes in CLDQ fatigue scores, SF-36 scores and Epworth Sleepiness scale scores between the rifaximin-α arm and placebo arm was minimal	To clarify, these were tertiary endpoints (ESS and SF36) for which the trial was never powered. Also, patients who had an episode of BOHE exited the trial (RFHE3001) as per the study protocol. Therefore, patients for whom QoL data were available at end of study were all in the covert (minimal HE) state as they were at the beginning of the study. Consequently, it cannot be expected (a priori) that statistically significant unadjusted differences in QoL would be detectable between baseline and last measurement. It is important to note that, because of altered mental and neuromotor status, it was not possible for subjects to complete the CLDQ, SF-36 and other QoL assessments during an overt HE breakthrough episode. Measurements would have been made after recovery from the overt episode. Therefore, as mental status was closer to baseline levels at the time of end of treatment assessments, QoL results may have been similar to baseline levels for subjects who had breakthrough overt HE episodes The planned statistical analysis did not take into account that patients at the end of the study would be those who never experienced a BOHE and was flawed in that respect. Post hoc analysis of CLDQ data (Sanyal et al 2011) showed significant improvement for rifaximin over placebo in all domains of disease-specific QoL and in 27 of 29 individual item responses. As we have previously stated, QoL is extremely difficult to measure in these patients. For the following reasons: 4. Cognitive impairment whereas patients believe they are perfectly normal	Comments noted. The Committee understood that there are substantial challenges in capturing quality of life evidence in people with hepatic encephalopathy (see section 4.17).

Consultee	Comment	Response
	5. Generic measures e.g. SF36 6. Time weighted averages are the most useful way of capturing **Reference:** Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. Alimentary Pharmacology & Therapeutics 2011; 34: 853–61.	
Royal College of Nursing	**Introduction** The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Rifaximin for maintaining remission from episodes of hepatic encephalopathy. Nurses caring for people with hepatic encephalopathy reviewed the documents on behalf of the RCN.	Thank you for your comments.
	Appraisal Consultation Document – RCN Response The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: i) **Has the relevant evidence been taken into account?** The scope of the document addresses the "hard" evidence surrounding research trials however it fails to capture other aspects. Research based evidence regarding quality of life in people with hepatic encephalopathy is difficult to ascertain as they suffer a wide variety of cognitive issues and their ability to elucidate fluctuates according to a number of precipitating factors which was briefly mentioned. This has meant that we do not have a robust evidence base, however we see in our clinical practice that hepatic encephalopathy can have devastating effects on the individual and carer/ family quality of life. ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**	The Committee understood that hepatic encephalopathy has a profound impact on patients' daily activities and quality of life and a resulting impact on caregivers. The Committee noted comments that treatment with rifaximin could improve quality of life, and reduce morbidity and carer burden (see FAD section 4.1). It understood that there are substantial challenges in capturing quality of life evidence in people with hepatic encephalopathy (see FAD section 4.17). The Committee heard that lactulose was not well tolerated and that this

Consultee	Comment	Response
	Treatment with lactulose has been predicated on preventing constipation and reducing ammonia which can contribute to hepatic encephalopathy. As described people find lactulose a difficult medicine to tolerate; it is a sweet, sickly tasting liquid. It causes diarrhoea, faecal urgency and sometimes faecal incontinence. From the individual's perspective this raises issues of dignity and privacy plus the feeling of embarrassment and can hamper their quality of life as they do not wish to be far from a toilet. Rifaximin on the other hand is a tablet and appears to be well tolerated by those that are prescribed it. The "cost" of caring for a person with hepatic encephalopathy cannot be captured in monetary terms. These people and their families have to endure day in, day out disruption to their lives on many levels. Individuals with hepatic encephalopathy are unlikely to be able to work, which has financial implications for them and their families. Many are unable to be left alone as it is unsafe. This leads to carers/family members having to make sacrifices in relation to their own employment, education, financial security and wellbeing. Many become isolated and their relationship with their spouse (usually) is altered from partner to carer. Other costs that are unable to be quantified are the resource requirements both in primary and secondary care to support these people. Many carers report increased contact with GPs, district nurses and require ongoing supportive care in the community. A precipitation of hepatic encephalopathy necessitates admission to hospital; this normally requires an ambulance as they are unable to be brought to hospital by relatives due to the level of their hepatic encephalopathy. The cost of their inpatient stay (sometimes in an ITU environment) plus time to recuperate and review the impact of their treatment prior to discharge all need to be considered. Specialist nurses within secondary care can spend a large amount of time supporting both the individual and their carers as well as liaising with local services. Again many of these costs cannot be quantified but they are a drain on NHS resources due to the increased interdependency that occurs with increasing hepatic encephalopathy. iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Anecdotally we know that Rifaximin works, based on comments from our liver nurse colleagues across England and between centre to centre. We are also aware of this as we share care between tertiary and secondary hospitals for many liver patients. We consider that many of these patients will not benefit from a cost benefit analysis of their UKELD/MELD scores and whether these are improved by the use of Rifaximin. This is because group of patients tend to deteriorate from a liver function perspective unless other treatments are instigated. We consider that Rifaximin management clinically will help to improve quality of life for the patients by reducing hepatic encephalopathy. This can have a positive effect for the patients as they are more likely to improve with their nutrition, their cognitive abilities and	treatment is considered undignified. The Committee recognised the need for alternative treatment options for preventing episodes of hepatic encephalopathy (see FAD section 4.2). The Committee understood that hepatic encephalopathy has substantial effects on people's families and carers, including loss of income, and heard from the clinical expert that patients need constant supervision either from family or professional carers. The Committee understood that the costs associated with constant care from family members and professional carers could not be built into the economic model, and factoring them in would improve the cost effectiveness of rifaximin (see FAD section 4.21). The company's model included costs relating to healthcare appointments and hospital admissions (see FAD section 3.30). The Committee concluded that rifaximin was effective in preventing episodes of hepatic encephalopathy, although the long-term benefits associated with rifaximin were uncertain. The

Consultee	Comment	Response
	also have some opportunity to be able to organise their affairs. The effect on their quality of life needs to be taken into consideration as the effect of the disease can be debilitating and some liver patients may have fractured relationships as a result and may wish to mend this. Also they tend to be younger and may not have recognised up to this point that they need to get their affairs in order. There is also a positive effect for the family/carer as they feel benefit from caring for someone who has improved cognitive function.	Committee concluded that rifaximin could be associated with improved quality of life. (see FAD sections 4.4, 4.5 and 4.15).
	iv) **Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Thank you for your comments. The Committee considered whether the appraisal might be affected by any issues relating to equality (see FAD section 4.23). A separate Equality Impact Assessment form has been issued along with the Guidance.

The Department of Health confirmed that it had no substantive comments to make regarding this consultation.

Comments received from clinical experts and patient experts

Nominating organisation	Comment		Response
Dr Debbie Shawcross, clinical expert nominated by Norgine	Section 1 (Appraisal Committee's preliminary recommendations)	Since the last appraisal committee meeting held in October where I served as a Clinical Advisor, I have some additional relevant data to submit for the committee to consider. These are the results of a National Audit of Rifaximin use in 4 UK centres [King's College London, Newcastle, Liverpool and Portsmouth]. This audit included data on 170 patients with hepatic encephalopathy (HE) who were retrospectively studied 1 year prior and up to 1 year following commencement of rifaximin therapy. These "real world data" convincingly demonstrate the efficacy and clinical utility of the drug as a fundamental component of the armamentarium available to clinicians treating patients with HE. A power point presentation summarising the key data arising from this audit will be forwarded to the NICE HQ for review. In essence however, apart from showing a significant reduction in the severity of the HE Conn Score ($p<0.0001$) and hospitalisation rate ($p<0.0001$) following commencement of the drug, the drug also	Thank you for your comments and for the additional information. The Committee considered this additional information from the national audit of rifaximin (see FAD section 4.7).

Nominating organisation	Comment		Response
		impacted on the trajectory of disease progression in patients who survive >90 days and show significant reductions in the Child Pugh Turcotte, (p<0.0001) MELD (p=0.03) and UKELD scores (p=0.02).	
	Section 2 (The technology)	The results of the National Audit referred to above show that the drug was extremely well tolerated with only 4/170 patients reporting side effects [diarrhoea which resolved after 7 days, nausea , rigors and rash]. The rigors were likely related to concomitant infection rather than the drug. None of the 170 patients developed Clostridium Difficile infection. What did become apparent from the audit data was that only 30/170 were still on the drug at the last follow up as there were a large number of who dropped out within 3 months of follow up [31% died and 35% were transplanted]. Indeed, there are insufficient data at this time to perform robust 6 and 12 month analyses. This calls into question putting too much weight on the validity of reflecting upon a clinically plausible diminishing mortality benefit with rifaximin over time, excluding mortality benefit in the remission state and the use of a lifetime time horizon to capture all costs and benefits associated with rifaximin although there is no doubt that the greatest benefit of the drug may be obtained in the first 3 months of treatment. Patients listed for transplantation gain the most benefit from the drug.	The Committee noted that rifaximin is well tolerated, and that the greatest benefit of the drug may be obtained in the first 3 months of treatment (see FAD section 4.5).
	Section 3 (The company's submission)	I think the clinical efficacy of rifaximin has never been called into question by the hepatology community but it has been harder to robustly demonstrate the HRQoL and mortality benefits of the drug when considering RFHE3001 and 3002 trial data. I am therefore unclear how requesting estimates of utilities from SF-36 quality-of-life data collected from the RFHE3001 trial and mapped directly to the EQ-5D, using all observations in each relevant health state and adjusted for baseline utility will provide any further clarity here. What the national audit does robustly demonstrate is that the reduction in hospital admissions from a mean(SD) of 2.7(3.2) pre-rifaximin to 1(1.8) post; p<0.0001 will have huge cost savings for the NHS. Furthermore, the improvement in Child Pugh, MELD and UKELD in those surviving >90 days will favourably impact on the mortality benefit of the drug way in excess of 10% considering the 2 year survival rate of someone with Child Pugh C disease is 35% compared to B (57%) and A (85%).	The Committee concluded that rifaximin was effective in preventing episodes of hepatic encephalopathy, and understood that there are substantial challenges in capturing quality of life evidence in people with hepatic encephalopathy (see FAD section 4.4 and 4.17). The Committee considered that the most appropriate approach for deriving the utility scores was the analysis based on SF-36 data only (see FAD section 4.14). The Committee considered the results from the audits, and noted that they were subject to uncertainty, but concluded that rifaximin is likely to reduce hospital admissions and may shorten the length

Nominating organisation	Comment		Response
			of hospital stay.
	Section 4 (Consideration of the evidence)	In addition to my comments above, I think that 2 other key points need to be considered when reaching a FAD. Firstly, with regard to "Equalities considerations and social value judgements", any patient with hepatic encephalopathy (HE) is in my opinion a vulnerable adult. Indeed, patients enrolled into HE trials are considered to lack the capacity to consent and require special dispensation from ethics committees and a nominee to facilitate important clinical decisions. Therefore, denying these patients access to this drug may be adversely impacting on a vulnerable cohort of society who does not have the capacity or access to patient advocate groups to argue on their behalf. Secondly, the burden on carers needs to be considered in any consultation decision. Many of these patients' next of kin have to look after them 24 hours a day and are consequently unable to work or contribute financially otherwise to society. Most patients with cirrhosis and HE are unable to self-care or be employed and are reliant on state benefits compared to those with cirrhosis without HE.	The Committee noted the comment that people with hepatic encephalopathy should be considered vulnerable adults. It considered that its recommendations do not discriminate on the basis of any characteristics protected under the equalities legislation (see FAD section 4.23). The Committee understood that hepatic encephalopathy has substantial effects on people's families and carers, including loss of income, and heard specialist that patients need constant supervision either from family or professional carers. The Committee agreed that these costs could not be built into the model and factoring them in would reduce the ICER (see FAD section 4.21).
	Section 5 (Implementation)	No further comment	Noted.
	Section 6 (Proposed recommendations for further research)	No further comment	Noted.
	Section 7 (Related NICE guidance)	Bearing in mind that further clinical trials are being performed, this date is possibly too remote and I would favour review in 2016.	The guidance will be considered for review in 3 years after publication (see FAD section 7).
	Section 8 (Proposed date of review of guidance)		
	[Dr Shawcross also provided results from the Rifaximin-α National Audit – not reproduced here]		

Comments received from commentators

None

Comments received from members of the public

Role*	Section	Comment	Response
Health professional (NHS) 1	Notes	HE results in significant poor quality of life, attendance in OP, extended length of stay in hospital and frequent admission to hospital. It is an indication for liver transplantation. Therapies are dietary and lactulose, both significantly limited in efficacy and tolerability. Lactulose in particular has poor data for its efficacy in HE and is associated with poor compliance due to sickly taste and associated increased frequency of bowel motions which is difficult to maintain in the long term. Using liver transplantation to treat HE is not cost effective and as organ availability continues to remain static alternative therapies need to be considered. Rifaximin appears to be a major step forward. It seems severe to consider a need to change QALY data scores. It is our experience and audit experience from Bristol and several centres in the UK that length of stay and need for admission is significantly reduced by the use of this drug. I would urge NICE not to dismiss this important medication and if costs are a concern recommend review of efficacy after one month of the medication being prescribed and if there is no clinical or objective improvement then it should be discontinued.	Thank you for your comments. The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families. It heard that lactulose was not well tolerated and recognised the need for alternative options for preventing episodes of hepatic encephalopathy. The Committee noted comments from consultation that treatment with rifaximin could prevent readmissions to hospital; it concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay, and understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose (see FAD sections 4.1, 4.8 and 4.12). The Committee concluded that rifaximin was effective in preventing episodes of overt hepatic encephalopathy in the trial population, although the long-term benefits associated with rifaximin were uncertain (see FAD sections 4.4 and 4.5). The Committee understood that there are substantial challenges in capturing quality of life evidence in people with hepatic encephalopathy, but concluded that rifaximin may improve quality of life (see FAD sections 4.15 and 4.17).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
Health professional (NHS) 2	Section 1 (Appraisal Committee's preliminary recommendations)	Independent of quality of life benefits reducing hospital admissions is in itself a surrogate marker of improved quality of life in addition the quality of life of carers needs addressing.	Thank you for your comments. The Committee noted comments from consultation that treatment with rifaximin could prevent readmissions to hospital; it concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay, and understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose (see FAD sections 4.1, 4.8 and 4.12).
	Section 2 (The technology)	My use of both the 200mg formulation and 550mg formulation has resulted in no side effects approx 40 patients to date very well tolerated.	The Committee noted that rifaximin is well tolerated (see FAD section 4.21).
	Section 3 (The company's submission)	The number of transplants is correct. It is rare to transplant for recurrent episodic encephalopathy per se unless liver dysfunction severe. It should be understood that encephalopathy is not part of either MELD or UKELD which provide minimum listing scores for transplantation. Thus patients are cannot be listed and will have low priority if recurrent encephalopathy is their problem and liver function reasonably maintained.	Comments noted.
	Section 4 (Consideration of the evidence)	seems reasonable and accurate	Comment noted.
	Section 5 (Implementation)	ok	Noted.
	Section 6 (Proposed recommendations for further research)	none	Noted.
	Section 7 (Related NICE guidance)	This date is far too long into the future It should be as soon as company can deliver the added information requested. The drug works well in clinical practice on top of lactulose. For some patients with recurrent admissions it has transformed their daily life and that of their families.	The guidance will be considered for review 3 years after publication.

Role*	Section	Comment	Response
	Section 8 (Proposed date of review of guidance)	There is not one gastroenterologist nor hepatologist shame on you all surely you need one here!!!	The Committee includes a multidisciplinary group of experts across numerous fields. It received extensive input from clinical experts in hepatology, both during the Committee meetings and in consultation.
Health professional (NHS) 3	Notes	Hepatic Encephalopathy is an area where there have been few advances in the last 20 years since Sheila Sherlock made her first observations. The emergence of fatty liver disease as an important and common cause for cirrhosis has increased the number of patients presenting with intractable encephalopathy as a complication of portal hypertension. This is a common presentation of advanced fatty liver disease. A large number of these patients have comorbidity that makes them unsuitable for definitive therapy such as transplantation and therapeutic options such as Rifaximin provide symptomatic control and have very clearly reduced hospitalisation rates. The alternative is too desperate to consider, and the impact on patients, families and carers is enormous. Many patient's (and their family's) lives are ruined by intractable encephalopathy. The increased use of TIPS shunts for refractory variceal bleeding has created another cohort of (often young) patients who are often severely disabled with chronic encephalopathy. Many of these patients are ineligible for transplantation due to ongoing addiction issues with alcohol etc. Their use of hospital resource as clinicians battle to control the encephalopathy is enormous. Just this morning I have been emailed about a patient in Wales who has encephalopathy from a TIPSS put in to control variceal haemorrhage, but is unsuitable for a transplant. The patient has been semi-comatose and in hospital for 2-3 weeks already and has now lost all ability to manage for themselves independently. The cost of a Rifaximin prescription here is small compared to paying a lifetime of nursing home costs to care for a 48 year old man who can no longer toilet himself. Alternatives to Rifaximin are lacking a strong evidence base and more difficult to use, with a worse side effect profile than this drug. In addition this antibiotic has robust trial data published in a premier medical journal that supports its efficacy and suggests that regular prescription will reduce hospitalisation.	Thank you for your comments. The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families. It heard that lactulose was not well tolerated and recognised the need for alternative treatment options in preventing episodes of hepatic encephalopathy (see FAD sections 4.1 and 4.21). The Committee noted comments from consultation that treatment with rifaximin could prevent readmissions to hospital; it concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay, and understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose (see FAD sections 4.1, 4.8 and 4.12).

Role*	Section	Comment	Response
		In the UK hospitalisation with complications of liver disease yields some of the longest inpatient stays of all indications for admission, so avoidance of admission and community treatment is all important. I would ask that the NICE committee takes this into account in making their judgement. Liver disease is now the 5th most common cause of death in the UK and the 3rd most common cause of death under the age of 65ys. Rates of liver cirrhosis and mortality are rising and the morbidity and associated costs of treatment are enormous. Rifaximin is one tool that might help reduce the disability associated with chronic encephalopathy and prevent sequelae of chronic brain injury. There really is no realistic alternative to this drug at present.	
	Section 4 (Consideration of the evidence)	Most experts in the field would agree that notwithstanding the usual nit-picking, the Bass study provides a much more robust platform for decision making than a NICE committee usually has to consider (As perceived by someone who already has had experience of a NICE appraisal!)	The Committee concluded that RFHE3001 was appropriately conducted and relevant to UK clinical practice (see FAD section 4.3).
	Section 8 (Proposed date of review of guidance)	There is not one member of the specialist team with any real world experience of managing liver disease, the complications of liver disease, or encephalopathy. Although you have taken expert evidence I suspect there is a real lack of practical knowledge, and I suspect this has impaired your decision making. Context is vital here.	The Committee includes a multidisciplinary group of experts across numerous fields. It received extensive input from clinical experts in hepatology, both during the Committee meetings and in consultation.
Health professional (NHS) 4	Section 1 (Appraisal Committee's preliminary recommendations)	Very poor decision	Thank you for your comments.
	Section 2 (The technology)	OK	Noted.
	Section 3 (The company's submission)	ok	Noted.
	Section 4 (Consideration of the evidence)	Poor decision based on benefits to patients and less load on in-patient burden and even abrogating the need for transplantation	Comments noted.

Role*	Section	Comment	Response
	Section 5 (Implementation)	agree	Noted.
	Section 6 (Proposed recommendations for further research)	n/a	Noted.
	Section 8 (Proposed date of review of guidance)	More hepatologists required in my opinion	The Committee includes a multidisciplinary group of experts across numerous fields. It received extensive input from clinical experts in hepatology, both during the Committee meetings and in consultation.
Health professional (NHS) 5	Section 1 (Appraisal Committee's preliminary recommendations)	Rifaximin has clearly been shown to be effective reducing relapse of hepatic encephalopathy (HE). Hopefully, the QoL analysis will be forthcoming but those of us using the drug in clinical practice have seen considerable gains in QoL for patients and their carers. The scenario analysis of diminishing mortality benefit presented by NICE looked over-simplistic and the optimistic survival data did not accurately reflect prognosis of decompensated cirrhosis as reported in several large hepatology studies.	Thank you for your comments. The Committee concluded that rifaximin was effective in preventing episodes of hepatic encephalopathy, although the long-term benefits associated with rifaximin were uncertain. The Committee concluded that rifaximin could be associated with improved quality of life (see FAD sections 4.4, 4.5 and 4.15). The Committee considered in detail the possible effect of rifaximin on mortality. The Committee concluded that although a mortality benefit had not been seen in the RFHE3001 study, 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 concluded that the magnitude of the effect is uncertain (see FAD section 4.18).
	Section 2 (The technology)	The technology summary seems accurate, although the listed "common" adverse reactions are difficult to attribute to rifaximin and are certainly not common in clinical practice. Several of the adverse effects listed are more likely manifestations of chronic liver disease or concomitant lactulose use.	The Committee noted that rifaximin is well tolerated (see FAD section 4.21). The listed adverse reactions reflect those listed in the Summary of Product Characteristics.

Role*	Section	Comment	Response
	Section 3 (The company's submission)	I would support the manufacturer's contention that the comparison should be with lactulose rather than neomycin. Neomycin is very rarely used due to concerns about absorption and side effects particularly nephrotoxicity. Lactulose itself has considerable adverse effects and diminishes quality of life through the incidence of diarrhoea, flatulence and abdominal discomfort.	The Committee concluded that neomycin was not an appropriate comparator for this appraisal. The Committee heard that lactulose was not well tolerated and recognised the need for alternative treatment options for preventing episodes of hepatic encephalopathy (see FAD section 4.2).
	Section 4 (Consideration of the evidence)	Rifaximin has been widely used throughout Europe for many years and several of us in the UK have built up clinical experience using the agent. Since 2010, I have treated around 50 patients with chronic HE in Portsmouth and have found that the agent does reduce hospitalisation. We recently submitted an abstract to the European Association for the Study of the Liver (EASL) annual meeting documenting our experience. We included all patients commenced on rifaximin between May 2010and November 2012.Data were analysed for 6 months prior to rifaximin and at 3, 6 and 12 months later. There were 42 patients, 62% male, mean age 59. Mean baseline scores were Child's-Pugh 9.4 (SD 2.1), MELD 15.0 (SD 7.9), UKELD 51.2 (SD 5.1). Survival at 3, 6 and 12 months was 78%, 67% and 62%. There was significant reduction in Child's-Pugh at 3 and 6 months (p< 0.01) but not 12 months and no change in MELD or UKELD. Comparing 6 months pre/post rifaximin, hospitalisation days fell from 233 to 143, a mean of 5.6 per patient, representing ?1,829 tariff costs. Admission episodes fell from 25 to 11.	Thank you for the additional information. The Committee noted comments from consultation that treatment with rifaximin could prevent readmissions to hospital, and considered information from audits of rifaximin (see FAD sections 4.1 and 4.7). It concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay, and understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose (see FAD sections 4.8 and 4.12).
	Section 5 (Implementation)	N/A	Noted.
	Section 6 (Proposed recommendations for further research)	N/A	Noted.
	Section 7 (Related NICE guidance)	This date seems too far ahead and, given the lack of alternatives to rifaximin, an earlier review would be welcomed.	The guidance will be considered for review 3 years after publication.

Role*	Section	Comment	Response
	Section 8 (Proposed date of review of guidance)	Surprising lack of liver disease experts on the panel.	The Committee includes a multidisciplinary group of experts across numerous fields. It received extensive input from clinical experts in hepatology, both during the Committee meetings and in consultation.
Health professional (NHS) 6	Section 1 (Appraisal Committee's preliminary recommendations)	In our centres experience Rifaximin reduced the number of hospital admissions, backed up by our audit data, and anecdotally has a quality of life benefit to our patients.	Thank you for your comments. The Committee noted comments that treatment with rifaximin could improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden (see FAD section 4.1). It concluded that rifaximin could be associated with improved quality of life and that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay (see FAD sections 4.8 and 4.15).
	Section 2 (The technology)	We have found that Rifaximin is very well tolerated, and perhaps compliance is improved and has in part a role to play in its efficacy (compare with the side effects of lactulose)	The Committee noted that rifaximin is well tolerated (see FAD section 4.21).
	Section 3 (The company's submission)	We audited our cohort of patients on Rifaximin and found that it reduced the number of hospital admissions and therefore inpatient costs/complications following the introduction of Rifaximin in our patients.	The Committee noted comments from consultation that treatment with rifaximin could prevent readmissions to hospital, and considered information from audits of rifaximin (see FAD sections 4.1 and 4.7). It concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay, and understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose (see FAD sections 4.8 and 4.12).
	Section 4 (Consideration of the evidence)	Aim: To evaluate the clinical benefit of using Rifaximin in end stage liver disease patients with hepatic encephalopathy as an adjunct to currently used modalities. Methods: Rifaximin use was audited in a single university hospital. An electronic database of patients who were receiving long-term treatment for hepatic	Thank you for the additional information.

Role*	Section	Comment	Response
		encephalopathy was obtained. Records were reviewed manually. Outcomes were total number of admissions with and without treatment and total length of stay per admission. Data was divided into patient months prior and after commencement of Rifaximin. Outcomes were compared and analysed for statistical significance using Mann-Whitney U Test. Results: 16 patients were selected. Mean age was 61 (range 42 to 73) years. Four had previously undergone TIPSS procedures. Hepatic encephalopathy was secondary to alcoholic liver disease (n=7), Non-Alcoholic Steatohepatitis (n=6), Hepatitis C (n=1), Autoimmune Hepatitis (n=1) and iatrogenic post splenic artery rupture repair (n=1). Patients had a combined 233 months on Rifaximin and 203 months off. The total number of admissions decreased from 2.2 per patient (range 0-11) prior to and 1 (range 0-8) after starting rifaximin ($p < 0.05$), average length of stay was 7.6 nights (1-58) and 4.9 respectively (1-26) ($p < 0.05$). This equates to 1.35 nights per month and 0.29 nights per month respectively for each patient prior to and following commencement of treatment.	
Health professional (NHS) 7	Section 1 (Appraisal Committee's preliminary recommendations)	Scotland has already taken on board a commitment to use rifaximin for the treatment of hepatic encephalopathy - Whilst there may not be an existing robust evidence base in clinical practice patients respond well to this therapy. Hepatic encephalopathy can have devastating effects for both patient and carers with frightening, often variable symptoms of disease and significantly overall reduced quality of life. This is costly to the NHS, not only in terms of hospital admissions but also in home visits by professionals such as GPs, practice nurses and paramedics.	Thank you for your comments. The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families. The company's model examined the effect of rifaximin on healthcare costs from the perspective of the NHS and Personal Social Services (see FAD sections 3.17 and 4.21).

Role*	Section	Comment	Response
	Section 2 (The technology)	Rifaximin is a well tolerated drug and out of 18 patients in Cornwall studies only one patient complained of mild abdominal pain and others experienced no side-effects. From a clinical perspective rifaximin clearly improves patient and carers quality of life and reduces hospital admissions.	The Committee noted that rifaximin is well tolerated (see FAD section 4.21). The Committee noted comments that treatment with rifaximin could improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden (see FAD section 4.1). It concluded that rifaximin could be associated with improved quality of life and that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay (see FAD sections 4.8 and 4.15).
	Section 3 (The company's submission)	It is difficult to quantify the cost of living day in and out with a disease such as HE- not only the acute service but also primary care services. Competing therapies include lactulose which is generally not well tolerated in high dosages and can bring on a myriad of problems and restrictions to lifestyle. Neomycin can be particularly nephrotoxic and it is vitally important to protect the liver patient also from a renal perspective.	The company's model examined the effect of rifaximin on healthcare costs from the perspective of the NHS and Personal Social Services (see FAD section 3.17). The Committee heard that lactulose was not well tolerated, and concluded that neomycin was not an appropriate comparator for this appraisal (see FAD sections 4.2 and 4.9).
	Section 5 (Implementation)	At present this drug is being used in clinical practice.	Comment noted.
Health professional (NHS) 8	Section 1 (Appraisal Committee's preliminary recommendations)	The department of gastroenterology at Royal Bolton Hospital has been using Rifaximin for just over a year now reflecting the Bass et al paper (N Engl J Med. 2010;362(12):1071)showing a reduction in hospitalisation with encephalopathy. We have found it effective and operate a database that reviews the efficacy on every patient. Even when efficacious our policy has been to withdraw it at 6 months and reassess. Our data has been very positive and was submitted as an abstract to the DDW 2014. We would be keen to see NICE approve rifaximin for the prevention of hepatic encephalopathy and would be more than happy to share our data.	Thank you for the additional information. The Committee noted comments from consultation that treatment with rifaximin could prevent readmissions to hospital, and considered information from audits of rifaximin (see FAD sections 4.1 and 4.7). It concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay, and understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose (see FAD sections 4.8 and 4.12).
	Section 2 (The technology)	No comments	Noted.
	Section 3 (The company's submission)	No comments	Noted.

Role*	Section	Comment	Response
Health professional (NHS) 9	Section 4 (Consideration of the evidence)	As a clinical nurse specialist in hepatology I have worked with patients with ESLD for the last 30 years (previously as a ward sister on a liver unit) Hepatic Encephalopathy (HE) is one of the most challenging complications of end stage liver disease. It is often under diagnosed because it can be difficult to detect in a clinic visit when it is minimal and patients and their families are often impacted by it in terms of personality changes, loss of memory, difficulty in concentrating on simple tasks which may lead to loss of their occupation. When it becomes more overt then their families may have to become their carers and this can cause serious financial difficulties. A common comment from a carer is "this is not the man/woman I married" due to their personality changes people can become aggressive and difficult to manage refusing to take medications or to eat. All of which add to their decline. In patients who have failed lactulose therapy with repeated admissions and may have complex admissions as they can be difficult to manage in a ward where they are not compliant with treatment as well as being aggressive and at risk of hurting themselves by trying to get out of bed and leave the ward. In some cases they may need to be intubated and ventilated in Intensive Care in order to deliver care and for their own safety. Rifaximin reduces admissions, improves the patients quality of life and those of their family and carers as well, enabling them to be compliant with their nutrition and other medications to treat their liver disease. There has been no other treatment that has been this exceptional in the maintenance treatment of HE. It has slowed down patients progression of their disease and it would be a backward step in the care of these patients if NICE didn't approve this medication for this indication. Chronic liver disease can be a very slowly progressive illness with many complications alongside HE such as variceal bleeding, spontaneous bacterial pertionitis, malnutrition which may require repeated admissions and outpatient clinic visits and rifaximin is clearly able to reduce HE admissions while improving quality of life.	Thank you for your comments. The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families (see FAD section 4.21). The Committee noted comments that treatment with rifaximin could improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden (see FAD section 4.1). It concluded that rifaximin could be associated with improved quality of life and that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay (see FAD sections 4.8 and 4.15).

Role*	Section	Comment	Response
Health professional (NHS) 10	Section 1 (Appraisal Committee's preliminary recommendations)	In clinical practice this is an invaluable drug to keep patients out of hospital, and in the case of post TIPS encephalopathy prevent closure of the shunt (and hence life-threatening GI bleed). I am using it currently in 3 patients who would otherwise require transplantation for encephalopathy. Quality of life improvements on this drug are profound and should not be underestimated by the appraisal committee.	Thank you for your comments. The Committee concluded that rifaximin was effective in preventing episodes of hepatic encephalopathy, although the long-term benefits associated with rifaximin were uncertain. The Committee concluded that rifaximin could be associated with improved quality of life (see FAD sections 4.4, 4.5 and 4.15).
	Section 4 (Consideration of the evidence)	Venous ammonia levels, asterixis & fatigue scores, SF-36 scores and Epworth Sleepiness scores are not valid end-points in determining the severity of encephalopathy. As we have no better hard end-points re-admission rates should be taken as gold-standard evidence.	Comments noted. The Committee considered information from audits of rifaximin (see FAD sections 4.1 and 4.7). It concluded that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay, and understood that the company's model predicted a reduced rate of hospital admission with rifaximin compared with lactulose (see FAD sections 4.8 and 4.12).
Health professional (NHS) 11	Section 1 (Appraisal Committee's preliminary recommendations)	There is no validated QoL measure for hepatic encephalopathy but there is obvious major clinical benefit seen in patients using the drug. I have no doubt it works and provides a major improvement on QoL for patients with encephalopathy.	Thank you for your comments. The Committee concluded that rifaximin was effective in preventing episodes of hepatic encephalopathy, although the long-term benefits associated with rifaximin were uncertain. The Committee concluded that rifaximin could be associated with improved quality of life (see FAD sections 4.4, 4.5 and 4.15).
	Section 2 (The technology)	no comments	Noted.

Role*	Section	Comment	Response
	Section 3 (The company's submission)	This in my view is overly complex and misses the point. Do clinicians see patients treated with this drug who's quality of life is revolutionised? Yes. If patients take it do they avoid hospitalisation-yes. The magnitude of benefit may be debated but it is a major change in a positive direction for patients and should be supported.	The recommendations are based on evidence of both clinical and cost effectiveness. The Committee noted comments that treatment with rifaximin could improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden (see FAD section 4.1). It concluded that rifaximin could be associated with improved quality of life and that rifaximin is likely to reduce hospital admissions and may shorten the length of hospital stay (see FAD sections 4.8 and 4.15).
	Section 4 (Consideration of the evidence)	see previous comments. This drug works and there is nothing else. It will be cost saving even taking the worst case.	Comments noted.
	Section 5 (Implementation)	no comments	Noted.
	Section 6 (Proposed recommendations for further research)	no comments	Noted.
	Section 7 (Related NICE guidance)	no comments	Noted.
	Section 8 (Proposed date of review of guidance)	no comments	Noted.
Health professional (NHS) 12	Notes	I have had several patients with crippling, resistant chronic encephalopathy whose lives, and those of their families have been transformed for the better by using rifaximin. It is a very useful drug for encephalopathy. My main concern is that its value may be eroded by its more trivial use for travellers' diarrhoea, which may lead to widespread resistance of bacteria.	Thank you for your comments.
	Section 1 (Appraisal Committee's preliminary recommendations)	In practical hepatology, it is a very useful drug, and transforms the lives of patients and their relatives/carers.	The Committee noted comments that treatment with rifaximin could improve quality of life (see FAD section 4.1).

Role*	Section	Comment	Response
	Section 2 (The technology)	It is well tolerated in my experience.	The Committee noted that rifaximin is well tolerated (see FAD section 4.21).
	Section 3 (The company's submission)	The manufacturer's evidence largely reflects experience with the drug in clinical practice. We only use it when there has been overt clinical encephalopathy which is non-responsive to lactulose.	The Committee concluded that RFHE3001 was appropriately conducted and relevant to UK clinical practice (see FAD section 4.3).
	Section 4 (Consideration of the evidence)	Chronic hepatic encephalopathy is demoralising and very expensive in use of NHS resources, as well as the time of carers. Rifaximin is the first breakthrough in this area for years, and may provide a useful bridge to other treatments such as transplant. With a hugely rising trend of liver disease in the UK, we badly need this drug to be available.	The Committee understood that hepatic encephalopathy has a profound impact on patients' 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 (see FAD section 4.1).
Health professional (NHS) 13	Section 1 (Appraisal Committee's preliminary recommendations)	It is going to take a long time to get this data. Many hepatologists have been using Rifaximin and have information on utility such as reductions in inpatients stays and admissions and need for community services, but unlikely to have formal quality of life assessment. This evidence should be assessed by appraisal committee.	Thank you for your comments. The Committee considered this information from audits of rifaximin use in clinical practice (see FAD section 4.7).
	Section 2 (The technology)	I have found Rifaximin very well tolerated in majority of patients with very few side effects.	The Committee noted that rifaximin is well tolerated (see FAD section 4.21).
	Section 3 (The company's submission)	The trial data is not exhaustive and company has tried to extract as much evidence of benefit that it can from studies. No data on high MELD patients who may gain significant benefit from rifaximin	The Committee noted that patients with more severe liver disease were excluded from the trial, but that the company had suggested that the trial results may apply to this group. The clinical experts stated that rifaximin would not generally be prescribed for these patients because it was unlikely to provide any meaningful benefit (see FAD section 4.3).
	Section 4 (Consideration of the evidence)	well considered	Comment noted.
	Section 5 (Implementation)	OK	Noted.

Role*	Section	Comment	Response
	Section 6 (Proposed recommendations for further research)	N/A	Noted.
	Section 7 (Related NICE guidance)	Rifaximin has already been used in clinical practise with real life benefits to improve patients quality of life, frequency of admissions, dependency. The delay to review will have significant impact on patients who are and may be in next deriving benefit. Also as increasing prevalence of chronic liver disease due to alcohol and obesity the loss of Rifaximin from therapeutic options will increase burden on secondary care with prolonged admissions with encephalopathy. An earlier review would be important	The Committee noted comments that treatment with rifaximin could improve quality of life, prevent readmissions to hospital and reduce morbidity and carer burden (see FAD section 4.1). The guidance will be considered for review 3 years after publication.
	Section 8 (Proposed date of review of guidance)	Needs more hepatology clinician input	The Committee includes a multidisciplinary group of experts across numerous fields. It received extensive input from clinical experts in hepatology, both during the Committee meetings and in consultation.
Health professional (NHS) 14	Section 1 (Appraisal Committee's preliminary recommendations)	As a Gastroenterology Consultant, who routinely treats patients with encephalopathy, I am disappointed that NICE are 'minded' not to approve Rifaximin. This is a very difficult condition, with limited treatment options and a considerable health impact. To prevent Rifaximin use would negatively impact on our ability to treat patients, as for many there are no real alternatives.	The Committee understood that hepatic encephalopathy is a serious condition with important and far-reaching effects on people with the condition and their families. The Committee recognised the need for alternative treatment options for preventing episodes of hepatic encephalopathy (see FAD sections 4.1 and 4.21).