Evidence Review Group Comments on 'Further Submission NICE STA: Hepatic encephalopathy - rifaximin (maintenance) [ID496]' Prepared by: Norgine Pharmaceuticals. 11th November 2014

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[redacted]

Introduction

Following a third NICE Appraisal Committee meeting for this STA in April 2014, Norgine has submitted further evidence for consideration. The Evidence Review Group (ERG) (SHTAC) was requested to provide an independent assessment of these analyses and received the submission on 12th November 2014. A response by Norgine to the ERG's clarification questions was received by the ERG on 8th December 2014. It should be noted that SHTAC was not the original ERG for this STA and has not participated in any of the previous Appraisal Committee Meetings. SHTAC has only assessed the evidence provided in the further submission, and by agreement with NICE prioritised for assessment the sections of the submission where the company had presented updated cost-effectiveness results (sections 1 and 2 – see next paragraph).

The further submission is divided into 4 sections: 1) The use of minimum important difference data to support the assumption of a utility gain for rifaximin-α; 2) the results of a series of 'real world' data audits on hospitalisation rates and length of hospital stay, 3) the effects of NHS policy on reducing hospital bed stay in England and Wales and 4) data to support the long term effectiveness of rifaximin-α. This report provides a critical appraisal of each section respectively.

1. Minimum important difference (MID) for assumption of utility gain in patients in the economic model

The ERG noted that the ICERs reported in the further submission (for example, base case with a lifetime horizon = £17,810) differed from those produced by the company's economic model provided to NICE on 11th November (for example, base case with a lifetime horizon = £17,834). They also noted that the ICERs in that model matched those in the previous written submission (for the meeting in April 2014). The ERG requested clarification from the company as to which of these ICERs was correct. The company confirmed that there was a mistake in the written submission due to a rounding error and to incorrect values in some of the cells of the model relating to age related-utility. The ERG presents the ICERs from the company's further submission document and the corrected ICERs in Table 1 of this document. There is a slight discrepancy between the two sets of ICERs.

Table 1. ICERs reported in the company's further submission and corrected ICERs

Covert Utility Assumption	Covert Utility Benefit	Lifetime ICER reported in the further submission	Corrected Lifetime ICERs
Norgine Basecase	0.106	£17,810	£17,834
Walters and Brazier (MID estimation)	0.074	£21,331	£21,302
Direct SF 36/EQ-5D Derived (TAC requested)	0.032	£28,805	£29,076

In their base case analysis, for the covert health state the company used utility values of 0.694 and 0.588 for patients treated with rifaximin-α and standard of care, respectively (NB. the covert state was described in the unpublished Final Appraisal Determination (FAD) (May 2014) as a 'remission state').This resulted in a utility increment of 0.106. A two-step approach was adopted to derive these utilities in which first the SF-36 data from the pivotal clinical trial RFHE3001[1] was converted to utilities. This was followed by quantifying the relationship between overall Chronic Liver Disease Questionnaire (CLDQ) score and the estimated utility. Incorporating these values, a lifetime ICER of £17,810 was obtained (Table 1 of company's recent submission).

To address concerns at the second Appraisal Committee Meeting (ACM), the company conducted sensitivity analysis using to obtain utility values from SF-36 data directly mapped to EQ-5D. This resulted in a utility increment of 0.032 for patients treated by rifaximin-α, producing an ICER of £28,805 for the lifetime horizon. In the further submission, the company has conducted a sensitivity analysis applying minimally important difference (MID) in utilities as described by Walters & Brazier.[2] This analysis was conducted because the company received feedback from various clinicians that rifaximin-α is associated with a noticeable improvement in health-related quality of life and in their opinion this was greater than the value of 0.032 and they therefore make the assumption that the utility benefit should be equivalent to a MID. A utility value of 0.074 from Walters & Brazier[2] was applied as the covert utility benefit which resulted in a lifetime ICER value of £21,331. Based on their analyses, the company concluded that using MID data reduced uncertainties around utility values and further established the hypothesis of utility gain in this patient group. Under these circumstances, they concluded that rifaximin-α is cost-effective compared to standard of care (ICER £21,331).

In general terms, MID can be defined as the minimum change in score in a domain of interest which could be treated as an important difference from a patient's perspective.[2-5] In their study, Walters and Brazier[2] compared the MID for two preference based measures of health: EQ-5D and SF-6D. They included 8 studies consisting of 11 patient groups in their analysis which were based on patients experiencing a wide variety of conditions such as leg ulcer, back pain, and early rheumatoid arthritis. Patients completed EQ-5D and SF-6D at two time points. In addition, they were also asked to rate their health based on a question of the SF-36 questionnaire. The score obtained in this process was used as an indicator of global rating of change (GRoC). The authors then used those patients who scored 2 or 4 in GRoC to estimate MID as the average change on EQ-5D and SF-6D scales. They then calculated the utility gain associated with the MID. Based on their analyses, the mean MID for EQ-5D was estimated to be 0.074 ranging from -0.011 to 0.140. The authors concluded that the wide confidence intervals for the EQ-5D MID estimates reflected uncertainty in the estimates and the small study sizes.

Norgine also reported a recent systematic review conducted by Coretti and colleagues[6] which reported different EQ-5D MID values from 17 publications. These studies included patients from a range of disease areas such as hip arthroplasty, rheumatoid arthritis, multiple myeloma, post-traumatic stress disorder, inflammatory bowel disease and plaque psoriasis. The reported EQ-5D MID values ranged from 0.03 to 0.52. Although values reported in this review were not used in the company' economic model, it was cited to provide justification for the relevant use of the EQ-5D MID value (0.074) from Walters and Brazier used in the economic evaluation.

1.1 ERG's critical appraisal

The ERG compared the characteristics of the 8 studies across 11 patient groups included in the analysis by Walters and Brazier with that of the RFHE3001 trial[1]. The following observations were noted:

- Of the 8 studies included by Walters and Brazier[2], none were based on patients with hepatic encephalopathy or patients with chronic liver diseases in general. Therefore the cited value might not be applicable in this patient group.
- The mean estimates for each of the 11 patient groups included by Walters and Brazier varied widely from the overall total mean MID EQ-5D estimate of 0.074 with a range of -0.011 to 0.140. This degree of uncertainty means the ERG cannot conclude that all disease types will have similar estimates for the utility gain associated with MID. As a

result, caution is advised in the interpretation of the company's assessment using the mean value.

- The mean utility increment preferred by the NICE Appraisal Committee (0.032) falls within the range of (-0.011 to 0.140) as reported by Walters and Brazier. The ERG cannot conclude which one of the two values (0.074 vs 0.032) would be the preferred estimate of MID as both the values fall within the specified range reported by Walters and Brazier. The current evidence does not provide any further information in this aspect.

Overall, the ERG is not convinced of the appropriateness of the MID estimate used in the company's submission. Due to the reasons cited above, there is a lack of robustness of the estimates used in the model. As a result, there is a considerable amount of uncertainty around the corresponding lifetime ICERs of £21,331 and £28,805 respectively as reported in the submission.

The ERG conducted a targeted search to identify any recent evidence published in 2013-14 on utility for rifaximin-α in the overt and remission health states, with no relevant studies identified. The ERG is not aware of any other significant methodological studies investigating MID in health technology assessment.

2. Use of UK "real world" data audits in the economic modelling

The original and revised economic models in the previous submissions used hospital admissions data from the pivotal RFHE3001 trial[1] (Table 2) to predict the proportion of patients who would be hospitalised when in the overt HE state. Length of inpatient stay was not measured in the trial and was estimated to be 5 days in both the rifaximin-α and placebo groups in the model, based on expert opinion. In section 2 of the further submission, the company presents meta-analyses of annual hospitalisation rates and length of inpatient stay (number of bed days per patient per year) before and after taking rifaximin-α based on independent "real world" data (RWD) from UK centres with experience in using rifaximin-α, to examine how using this data influences its cost-effectiveness. Estimates from the meta-analyses have been used in the economic model and the impact on the ICERs is presented and discussed. The ERG notes that the sponsor of the four included audits is unclear from the original sources.

The company states that a number of centres have carried out audits following use of rifaximin-α and refers the reader to Appendix C of the submission for a list of six relevant publications capturing data from six centres.

Table 2. Hospitalisation data from the pivotal RFHE3001 rifaximin-α trial and data used in the original and revised submission economic models

Source, length of follow-up	Reason for hospitalisation	Placebo	Rifaximin-α	HR, 95% CIs / statistical significance
Trial data				
RFHE3001 trial data,[1] 6 months	HE-related	13.6% [n = 19/140]	22.6% [n = 36/159]	HR 0.50, 95% CI 0.29 to 0.87
Data used in the economic model in the previous submissions				
Original submission - RFHE3001 trial data, 6 month probabilities [converted to monthly probabilities used in model, assuming constant hazard over time]	HE breakthrough episode	36/73 (49.32%) [10.71%]	19/31 (61.29%) [14.63%]	NS
Revised analysis – aggregated 6-month probability applied to both arms	HE breakthrough episode	52.88%, predicting 36 hospitalisations	52.88%, predicting 19 hospitalisations	-

CIs, confidence intervals; HE, hepatic encephalopathy; HR, hazard ratio; NS, not statistically significant.

Of these RWD audits, data from four UK centres (Dundee,[7] Bristol,[8] Newcastle[9] and Bolton[10]) were selected to be used in the meta-analysis on the basis that they were the first independently conducted UK audits to be published and that they contained data after "a minimum of exposure to drug of at least 6 months". Other than the requirement of at least a six month exposure to rifaximin-α, the company does not appear to have used explicit selection criteria for identifying relevant studies. (The ERG requested clarification from the company about how the searches and study selection were carried out and the company stated that formal searches had not been undertaken and the included audits were identified as key outputs from gastroenterology and hepatology academic meetings.)

The company additionally identified "King's" multicentre data[11] (including data from King's, Newcastle, Portsmouth and Liverpool – see Appendix C of further submission) and an audit from Portsmouth,[12] neither of which were used in the meta-analysis. The King's data was

excluded due to heterogeneity between centres included in it and because the duration was less than six months (it was 3 months). The ERG agrees with the company's decision to exclude the King's data, but on the grounds that it would have had to have been 'annualised' for inclusion in the meta-analysis and the ERG is not convinced of the validity of the method the company has used to 'annualise' data (see below). The ERG suggests that annualising the 3 month data may have led to misleading results. The Portsmouth data were not used because the audit was published only recently, but the company has referenced it for transparency and so it could be used in a sensitivity analysis. The company has provided the hospitalisation and bed days data from the Portsmouth audit in Appendix C of the further submission, but has not conducted sensitivity analyses. The ERG suggests that sensitivity analysis using these data would have been useful.

After the ERG received the further submission, the company submitted an academic-in-confidence abstract containing [redacted] The ERG has compared the findings [redacted] with the outcomes of the meta-analyses in the further submission and also carried out a scenario analysis using the data (results are provided below). The ERG therefore has not conducted a sensitivity analysis using the separate Portsmouth audit excluded from the meta-analysis in the further submission, [redacted].

All four of the audits included in the further submission were retrospective comparisons of hospitalisations and bed days before and after treatment with rifaximin-α. The company verified with the study authors that all patients in the audits were aged 18+ and had received rifaximin-α in line with its licence. Due to the availability of rifaximin-α at the time of the audits patients either received a total daily dose of 1100mg or 1200mg. The Bristol and Newcastle audits observed outcomes for a 12 month period before using rifaximin-α and a 12 month period after using rifaximin-α. Data from the Dundee and Bolton audits were annualised by the company, using a constant event rate assumption, because the observation time was less than 12 months. Additionally, data presented as medians and ranges in the Bolton study were transformed into means and SDs for use in the meta-analysis. The company presented a preliminary descriptive analysis of the annualised hospitalisation rates and bed days data

from the four audits to NICE in July 2014. The preliminary data are tabulated in Table 5 of the further submission and the data actually used in the meta-analysis are tabulated in Tables 6 and 7 of the further submission. Data are also tabulated in Appendix C (including data from the excluded King's and Portsmouth audits).

A continuous random effects model was used for the meta-analyses, to account for heterogeneity. The meta-analysis of hospital admissions resulted in a mean difference of 1.245 (95% CIs: 0.661, 1.829) hospitalisations per patient per year between before and after receiving rifaximin-α, favouring rifaximin-α. [redacted] The company assessed heterogeneity in each of the hospital admissions and bed days meta-analyses, and identified heterogeneity in the bed days meta-analysis only (I^2 = 63%, p = 0.043, which the ERG notes indicates substantial heterogeneity[14]). To address this, the company conducted a sensitivity analysis where data from the Bolton audit were excluded. The mean differences in bed days per patient per year found in both meta-analyses presented in the further submission and calculated by the ERG from [redacted] are shown, along with the corresponding ICERs, in Table 3. The table presents the ICERs for a model using a covert (remission) utility value of 0.032 (the NICE Appraisal Committee preferred estimate) and a lifetime horizon; see Table 9 of the further submission for the full range of ICERs reported by the company for different utility benefits and time horizons.

Table 3. Summary of bed days per patient per year data from the meta-analyses and the [redacted], and the resulting ICERs

Data source	N in analysis	Before rifaximin-α, mean bed days per patient per year	After rifaximin-α, mean bed days per patient per year	Mean difference (95% CIs, where available)	Lifetime ICER (£/QALY), using covert utility benefit of 0.032
Meta-analysis of 4 RWD sources provided in further submission	79	-	-	22.184 (9.095, 35.273)	11,654
Meta-analysis of RWD sources – sensitivity analysis excluding Bolton, provided in further submission	55	-	-	16.543 (9.084, 24.003)	16,276
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	19,791[1,2]

ICERs, incremental cost-effectiveness ratios; RWD, real world data. [redacted] [2]ICER calculated by the ERG using the corrected economic model.

The ERG notes that the confidence intervals around the mean differences derived from the further submission meta-analyses are wide and the company has provided ICERs in Table 9 of the further submission for the lower and upper bound 95% CIs, in addition to the means. These data indicate considerable uncertainty in the ICERs. For example, in a model using the mean difference in bed days estimated from the sensitivity analysis excluding the Bolton audit and using a covert utility increment of 0.032, across the lower and upper confidence intervals, the ICERs range from £25,425 to £6,869. The scenario analyses run by the ERG using [redacted] show that for the Norgine basecase (covert utility benefit 0.106 and lifetime horizon), the ICER is £12,139. For the NICE Appraisal Committee preferred utility gain estimate of 0.032 and a lifetime horizon, the ICER is £19,791.

2.1 ERG's critical appraisal

The ERG considers that there is considerable uncertainty around the hospitalisation and bed days estimates derived from the company's meta-analyses of the RWD audits and their generalisability to clinical practice. The main issues are:

- The company has not specified details of any searches to identify audit data, nor fully explained the a priori eligibility criteria used to select studies for inclusion in the meta-analysis (beyond a requirement of a six month duration minimum). The company's response to the ERG's clarification question was that no formal literature searches were undertaken. It is therefore unclear whether all relevant real world audit data sources have been included. The ERG undertook targeted searches (see Appendix 1 for details of the searches) and did not identify any additional UK studies.
- Literature indicates that length of hospital stay per overt HE admission is typically around 5 days.[15-18] This is substantially lower than the [redacted] and [redacted] days per admission used in the model in the further submission for placebo and rifaximin-α, respectively.
- The company has provided no details about the characteristics of the patients included in the audits or the exact treatment they received before rifaximin-α, except that all patients were aged 18 or over. The ERG has data extracted some of the limited information available about the patients from the original sources (which are all conference abstracts) and their treatment (see Appendix 2). Patients were, on average, older than those in the RFHE3001 trial, but had generally similar MELD scores. The company notes in the further submission that rifaximin-α was used in the majority of the patients in the audits to reduce the risk of a recurrent overt HE episode in those who had had at least one previous episode. Given the lack of information about the patients, it is unclear how representative they are of those in whom rifaximin-α may be used if it is approved for more widespread use in the NHS. Therefore the currently available RWD audits may

only provide data on hospital admissions and length of bed stay for a particular (unknown) subsample of patients. The company does not discuss this issue in the further submission.

- The observational data available from each audit is based on small sample sizes (ranging from four to 27 patients per centre). The ERG notes that there are wide confidence intervals around the estimates of mean differences in hospitalisations and bed days per patient per year in both of the main meta-analyses and also in the sensitivity analysis of bed days. This indicates much uncertainty about where the true mean difference lies, probably due to the small sample sizes in each of the audits.
- There is no information in the submission or original sources about whether the hospitalisations were all-cause or HE-related. Data used in the original and revised submissions were for HE-related hospitalisations.
- The ERG is not convinced of the validity of the constant event rate assumption the company used for annualising the Bolton and Dundee data. In its clarifications request to the company, the ERG asked for a justification for the use of this assumption. The company stated that without access to the raw data from the audits, the assumption was considered a reasonable one to use and provided no further justification. The ERG did not have access to expert opinion during the appraisal of the further submission to inform a judgement about the appropriateness of this approach. However, data from the Portsmouth and Bristol audits, where six month data are available in addition to 12 month data, do not support that this was a reasonable assumption to apply to the bed days data (see Appendix 3 for the 6 and 12 month data from the Portsmouth and Bristol audits).
- The company has used a random effects meta-analysis rather than a fixed-effect analysis and the ERG notes that in the presence of small sample sizes, such as in the RWD audits used in the submission, a random-effects approach may not be conservative, as it is likely to estimate a more beneficial treatment effect than a fixed-effect model would if small studies find the intervention treatment is beneficial.[14] The company has not presented results for fixed-effect models and the ERG suggests this would have been a useful sensitivity analysis to conduct to assess if both approaches produced similar outcomes.
- Outcomes from observational before- and after- studies where patients are their own controls may be influenced by time and context. Observational data provide weaker evidence than RCT data, particularly in the context of small participant numbers and uncertainty about how representative the participants included were of the wider HE population.

[redacted]

In addition to the main issues with the data described above, the ERG identified the following, more minor issues which contribute to uncertainty, particularly in relation to the accuracy of the bed stays data:

- The company has provided numerical data from the RWD audits in three different places in the further submission. The ERG has checked all these data against each other and against the original sources for consistency. Some discrepancies in data between the sources were identified. Overall, from these checks, the ERG considers only the discrepancies in bed days data for the Dundee audit between Tables 5 and 7 in the further submission to be a concern and to have potential to impact on the outcome of the meta-analysis (Appendix 3 shows how these data differ). It is unclear from the submission why the data differ (the ERG sought clarification from the company, but the company did not provide an explanation for the discrepancy in their response).
- The ERG agrees with the company's decision to conduct a sensitivity analysis of the bed days meta-analysis by excluding the Bolton audit. The ERG suggests that the transformation of the original Bolton data into means and SDs for use in the meta-analysis and the application of the constant event rate annualisation assumption to these transformed means may have resulted in inflated and inaccurate differences in bed days (and therefore contributed to heterogeneity). Therefore, the ERG suggests that the sensitivity analysis excluding Bolton (Figure 3 in the further submission) provides a better estimate of mean differences in bed days than the meta-analysis of data from the four RWD centres.

2.2 Summary

Overall, the ERG suggests that the RWD from the audits and subsequent estimates of mean differences in hospitalisations and bed stays, and the subsequent modelled cost-effectiveness estimates are subject to limitations and uncertainties. The ERG is especially concerned that the data may not fully reflect clinical practice if rifaximin-α is approved for use in the NHS, because it is unlikely to be representative of all patients who would be seen in practice. The ERG considers that the company has not provided sufficient explanation in the further submission about how these data improve on those previously used to estimate hospital admissions (in the pivotal clinical trial) and bed days (based on expert opinion), other than the fact that they represent real world clinical practice. If the Committee decides to accept the ICERs based on the mean differences found in the meta-analyses in the

further submission, the ERG suggests that the ICER derived from the lower bound confidence interval estimates of differences in bed days in the sensitivity analysis excluding Bolton is likely to be the most conservative (ICER of £25,425 when using a covert utility increment of 0.032 and a lifetime horizon). Alternatively, the ICERs estimated by the ERG based on [redacted] (ICER of £19,791 when using a covert utility increment of 0.032 and a lifetime horizon).

3. Analysis of the effects of NHS policy in England & Wales on reducing hospital bed stay

The further submission refers to comments made at the third Appraisal Committee Meeting regarding observed reductions in hospital admissions and bed days associated with treatment with rifaximin-α, based on real world audit data from specialist hepatology centres. Specifically, it was noted that these reductions may have been caused by strategies to improve NHS resource use more generally, rather than due to the effect of rifaximin-α. The company therefore analysed hospital episode statistics (HES) to investigate any effect of these strategies. (NB. The evidence cited is not used to inform updated cost-effectiveness estimates in the submission).

Appendix A of the further submission provides a brief analysis of HES for the period 2010 to 2013, coinciding with just before the start of the audit periods and the end period of the audits presented to the Appraisal Committee in 2013. The analysis is based on a selection of 16 Healthcare Resource Group (HRG) codes for hepatology-related disorders. None of the codes relate specifically to hepatic encephalopathy, so the data relate to liver disease more broadly. The mean and median lengths of stay presented are similar for the period studied (e.g. mean ranging from 7.51 to 8.15), showing no marked decrease. The company cite feedback from (unspecified) hepatology centres in England and Wales who confirmed that strategies to reduce bed stay in their hospitals were introduced *prior* to the audit periods. However, the submission also states that feedback from specialist hepatology centres (again, unspecified) indicated that they were not targeted for strategies to reduce hospital stay.

The submission does not present equivalent HES data for a longer time period prior to 2010 to put the analysis into context (e.g. to show any trends or fluctuations in bed days over time). The extent to which rifaximin-α was in use for hepatic encephalopathy in clinical

practice during the audit period is also unclear. Overall, the ERG considers that the brief data presented should be interpreted as illustrative rather than definitive, due to the uncertainties raised above.

4. Long term effect and effect on mortality of rifaximin-α

The further submission provides evidence in support of the long-term effect of rifaximin in terms of reducing recurrence and hospitalisations, and also evidence to suggest a reduction in mortality. The evidence cited is not used to inform updated cost-effectiveness estimates in the submission.

a) Further data to support the long term effect of rifaximin-α

The company provides evidence to show the long term effect of rifaximin. The company does not describe how they have searched for supporting studies and whether these were identified through a systematic search.

The company states that the results of the RFHE3002 open label study[19] demonstrated the long-term effect of rifaximin-α and RWD audits, previously presented to the committee, showed a consistent reduction in hospitalisations for longer than 6 months. Furthermore they state that the long-term efficacy of rifaximin is also supported by publications from other countries.(Vlachogiannoakos,[20] Hanouneh,[21] Confer,[22] Neff,[23] Irimia[24]).

Of the 5 studies cited, only 1 appears to support the company's statement that rifaximin has a long term treatment effect on hospitalisation beyond 6 months (Irimia et al.[24]). Of the other studies cited, some were in a patient population that did not have hepatic encephalopathy or did not provide information on hospitalisation (Vlachogiannoakos,[20] Hanouneh,[21] Confer[22], Neff et al.[23]). Mullen et al[19] provided information on hospitalisation, reported at 6 months. The ERG has provided a critical appraisal of the real world audits in section 2.

Irimia et al.[24] included 78 patients who had recovered from hepatic encephalopathy were treated with either lactulose only (n=10), rifaximin intermittently (n=38), or rifaximin daily (n=28) for 6 months. Patients were followed-up for 12 months. A total number of 26 HE-related hospitalisations were recorded during follow-up. The frequency of HE-related hospitalisations was significantly lower for the rifaximin intermittent and daily groups (31.57% vs 28.57%) than in the lactulose only group (50%). The ERG notes the small number of patients in each of the groups which may limit reliability of the results.

The ERG considers that the company has provided limited relevant evidence to support the long term efficacy of rifaximin with respect to hospitalisation.

b) Effect on mortality of treatment with rifaximin-α

The NICE Appraisal Committee had previously noted that an initial mortality benefit associated with rifaximin was plausible, however the magnitude and duration of the effect was considered uncertain. The company provides further evidence to support the mortality benefit of rifaximin-α in this patient group.

Four studies are briefly discussed in the further submission.[17;20;23;25] It is reported that a review of mortality studies in hepatic encephalopathy was conducted as part of previous submissions. However it is not clear if these studies were previously identified as no details were provided on the identification process of these studies.

The studies by Neff and colleagues[23] and Sharma and colleagues[17] were based on patients with overt hepatic encephalopathy which the ERG considers as relevant sources. Neff and colleagues[23] conducted a retrospective analysis on 185 US patients with an aim to report long-term survival data. The patients were sub-divided into four groups receiving: lactulose (n=58); lactulose and rifaximin (n=55); rifaximin (n=28); and none (n=44). Survival rates for each of these groups were reported at 6 months, 1 year and 3 years. The analysis showed mortality benefit to be highest for patients receiving rifaximin-α alone, followed by those receiving lactulose and rifaximin-α (for details, see Table 4). Despite its relevance only an abstract was available so it is not possible to fully assess its methodological quality. Of note the study is retrospective. It is based on US population, therefore the generalizability of the results to the UK remains unclear.

Sharma and colleagues[17] conducted a prospective double-blind randomised controlled trial with 120 patients in two arms receiving lactulose plus rifaximin (n=63) and lactulose plus placebo (n=57). The trial was conducted over a 2 year time-period. The authors concluded that patients treated with lactulose plus rifaximin had a significantly lower mortality rate (23.8%) compared to those treated with lactulose and placebo (49.1%). This difference in mortality rate between the two arms was found to be statistically significant (see Table 5).

The remaining two studies were not based on patients with hepatic encephalopathy:[20;25] the study by Vlachogiannakos and colleagues[20] was based on patients with decompensated

alcoholic cirrhosis and ascites whereas the study by Kimer and colleagues[25] were based on those with advanced liver disease (cirrhosis). As a result, the ERG considers this evidence is an inappropriate source on which decisions on mortality benefit of rifaximin cannot be based.

Table 4. Survival rates reported by Neff and colleagues[23]

Time point	Lactulose	Lactulose/Rifaximin	Rifaximin	None
6 months	60%	65%	76%	45%
1 year	46%	54%	63%	35%
3 years	29%	41%	51%	12%

*Lactulose vs Lactulose/Rifaximin: p value=0.057; **Lactulose vs Rifaximin: p value= 0.049

Table 5. Mortality data reported by Sharma and colleagues[17]

	Lactulose+Rifaximin	Lactulose+Placebo	
Mortality	23.8%	49.1%	p<0.05

Based on the evidence provided, the ERG considers there is some evidence to support the company's argument that rifaximin-α has a mortality benefit of up to 3 years.

5. Summary

1. The use of minimum important difference data to support the assumption of utility gain

The company considers that the utility benefit of rifaximin-α compared to standard of care is greater than the value derived by mapping trial utility data from SF-36 to EQ-5D (0.032). The company suggests that rifaximin-α provides an observable clinical benefit in patients and therefore the utility benefit should be equivalent to a minimum importance difference (MID). Using the mean MID utility value from a study by Walters and Brazier of 0.074 produces an ICER of £21,331 per QALY.

Overall, the ERG is not convinced of the validity of the MID estimate used in the company's submission. The study by Walters and Brazier contained no patients with hepatic encephalopathy or other liver diseases. The values estimated for MID varied widely and there is considerable uncertainty as to an appropriate value to use for MID for this population.

2. Use of UK “real world” data audits in the economic modelling

The original and revised economic models in the previous submissions used hospital admissions data from the pivotal RFHE3001 trial. In the further submission the company presents meta-analyses of annual hospitalisation rates and length of inpatient stay (number of bed days per patient per year) before and after taking rifaximin-α using independent “real world” data from UK centres with experience in using rifaximin-α. Data from four UK centres (Dundee, Bristol, Newcastle and Bolton) were selected to be used in the meta-analysis. After the ERG received the further submission, the company submitted [redacted]

The meta-analysis of hospital admissions resulted in a mean difference of 1.245 (95% CI: 0.661, 1.829) hospitalisations per patient per year between before and after receiving rifaximin-α, favouring rifaximin-α. [redacted]

The meta-analysis of bed days resulted in a mean difference of 22.184 (95% CI: 9.095, 35.273) favouring rifaximin-α. The lifetime ICER based on this mean difference was £11,654 using the covert health state utility increment of 0.032. There was statistically significant heterogeneity in the bed days meta-analysis, and the company conducted a sensitivity analysis where data from the Bolton audit were excluded. In this sensitivity analysis the mean difference was 16.543 (95% CI 9.084, 24.003). The corresponding lifetime ICER was £16,276 (utility increment 0.032). [redacted] The ERG conducted a scenario analysis using this data and the lifetime ICER was £19,791 (utility increment 0.032).

The ERG considers that there is considerable uncertainty around the hospitalisation and bed days estimates derived from the company’s meta-analyses of the RWD audits: there is little detail given about the characteristics of the patients included in the audits; the audit data is observational (no separate comparison group) and retrospective; there are small numbers of patients included; there are wide confidence intervals around the estimates of mean differences; there is a lack of clarity how some of the audit data were transformed into annualised estimates for inclusion in the meta-analysis; [redacted] If the Committee decides to accept the ICERs based on the mean differences from the meta-analyses in the further submission, the ERG suggests that the ICER derived from the lower bound confidence interval estimates of differences in bed days in the sensitivity analysis excluding

Bolton is likely to be the most conservative (ICER of £25,425 when using a covert utility increment of 0.032 and a lifetime horizon). [redacted]

3. Analysis of the effects of NHS policy in England & Wales on reducing hospital bed stay

The company reports that at the third Appraisal Committee Meeting it was noted that reductions in hospital admissions and bed days associated based on real world audit data from specialist hepatology centres may have been influenced by strategies to improve NHS resource use more generally, rather than due to the effect of rifaximin-α.

The further submission provides a brief analysis of hospital episode statistics for the period 2010 to 2013, coinciding with just before the start of the audit periods and the end period of the audits presented to the Appraisal Committee in 2013. The mean and median lengths of stay presented are similar for the period studied (e.g. mean ranging from 7.51 to 8.15 days), showing no marked decrease. These data were based on healthcare resource codes for chronic liver disease rather than specific to hepatic encephalopathy. No updated cost effectiveness estimates are provided in the submission. Overall, the ERG considers that the brief data presented should be interpreted as illustrative rather than definitive.

4. Data to support the long term effectiveness of rifaximin-α

The company reports data to support the long term effectiveness of rifaximin-α on hospitalisations and mortality, but does not provide any updated cost effectiveness estimates. The ERG considers that of the relevant evidence submitted, there was limited evidence to support the long term efficacy of rifaximin-α with respect to hospitalisation, but there was some evidence to support the mortality benefit of rifaximin-α up to 3 years.

References

(1) Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB et al. Rifaximin treatment in hepatic encephalopathy. *The New England Journal of Medicine* 2010; 362(1071):1081.

(2) Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Quality of Life Research* 2005; 14:1523-1532.

(3) Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin.Trials. 10[4], 407-415. 1989.

(4) Landorf KP, Radford JA, Hudson S. Minimal Important Difference (MID) of two commonly used outcome measures for foot problems. Journal of Foot and Ankle Research 3[7]. 2010.

(5) Cook A. Clinimetrics Corner: The Minimal Clinically Important Change Score (MCID): A Necessary Pretense. The Journal of Manual & Manipulative Therapy 16[4]. 2008.

(6) Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ 5D index: a critical review. *Expert Review of Pharmacoeconomics & Outcomes Research* 2014; 14:221-233.

(7) Real world experience of rifaximin in hepatic encephalopathy. Falk Symposium No 191 Liver Diseass in 2013: Advances in Pathogenesis and Treatment; London: Falk Foundation eV; 2013.

(8) Rifaximin treatment in hepatic encephalopathy - a single centre experience. 2012.

(9) Orr J, Perez F, Mitchison H, Hewett M, Saksena S, Topping J et al. Rifaximin for hepatic encephalopathy is cost effective at reducing emergency hospital admission. *Gut* 2013; 62(Suppl 1):A91-A92.

(10) Goel A, Patel N, Blackwell R, Crompton S, Moriarty KJ. Rifaximin treatment in hepatic encephalopathy (HE) - marked reduction in hospital admissions and hospital bed day occupancy in a UK district general hospital. *Gut* 2014; 63(Suppl 1):A179-A180.

(11) Patel VC, Orr J, Sturgeon J, Habtemariam Z, Preedy H, Richardson P et al. Rifaximin is efficacious in the treatment of chronic overt hepatic encephalopathy: a UK liver multi-centre experience. *Gut* 2014; 63(Suppl 1):A14-A15.

(12) Real world experience of rifaximin for hepatic encephalopathy: effective maintenance of remission and reduced hospital admissions in a large secondary care cohort. BASL; 2014.

(13) [redacted]

(14) Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011. The Cochrane Collaboration.

(15) Neff GW, Kemmer N, Zacharias VC, Kaiser T, Duncan C, Jonas M et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. *Transplantation Proceedings* 2014; 38(10):3552-3555.

(16) Leevy CB, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for

the treatment of hepatic encephalopathy. *Digestive Diseases and Sciences* 2007; 52(3):737-741.

(17) Sharma BC, Sharma P, Lunia MK, et al. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol* 2013; 108:1458-1463.

(18) Neff G, Kemmer N, Parkinson E, Cece E, Christian M, Webster H et al. Outcomes in length of hospital stay in cirrhotics admitted for overt hepatic encephalopathy. *American Journal of Gastroenterology* 2012; Suppl 107:S601.

(19) Mullen KD, Sanyal AJ, Bass NM, et al. Rifaximin is Safe and Well Tolerated for Long-Term Maintenance of Remission from Overt Hepatic Encephalopathy. *Clin Gastroenterol Hepatol* 2013; 12:1390-1397.

(20) Vlachogiannakos J, Viaziz N, Viasianopoulos P, et al. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol* 2013; 28:450-455.

(21) Hanouneh MA, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R et al. The role of rifaximin in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. *J Clin Gastroenterol* 2012; 46(8):709-715.

(22) Confer B, Theethira T, Dugum M, et al. Rifaximin in Addition to Standard medical Therapy Significantly Reduces The Time to First Esophageal Variceal Bleed. *Gastroenterol* 2014; 146 (Suppl 1)(Abstract):S-93-S-94.

(23) Neff G, Christian M, Ramirez M. Long-term survival following overt hepatic encephalopathy. *American Journal of Gastroenterology* 2012; 107(Suppl 1):Abstract 1516.

(24) Irimia R, Trifan A. Efficacy of rifaximin versus lactulose for reducing the recurrence of overt hepatic encephalopathy and hopitalizations in cirrhosis. *Rev Med Chir Soc Med Nat Iasi* 2012; 116(4):1021-1027.

(25) Kimer N, Krag A, Moller Seal. Systematic Review with Meta-Analysis: the effects of rifaximin in hepatic encephalopathy. *Aliment Pharmacol Ther* 2014; 40:123-132.

Appendix 1

Details of ERG targeted searches to identify other RWD audits which have not been included in the further submission

Searches conducted 21/11/14

Conference	Abstracts published in	Results
British Society for Gastroenterology June 2014	Gut 63, Suppl1	http://gut.bmj.com/content/63/Suppl_1.toc 16 hits for 'rifaximin' • Goel et al (Bolton) (included in submission) • Patel, Orr et al (4 centre analysis, but 3 months period, excluded by company)
June 2013	Gut 62, Suppl1	http://gut.bmj.com/content/62/Suppl_1.toc 5 hits for 'rifaximin' • Orr et al (Newcastle) (included in submission)
EASL April 2014	Journal of Hepatology 60, Suppl 1	www.journal-of-hepatology.eu/issue/S0168-8278(14)X0004-8 7 hits for 'rifaximin' None relevant
April 2013	Journal of Hepatology 58, Suppl 1	9 hits for 'rifaximin' None relevant
BASL September 2014	Google search for BASL and rifaximin	Nothing relevant
AASLD November 2014	Hepatology 60, S1	http://onlinelibrary.wiley.com/doi/10.1002/hep.v60.S1/issuetoc None relevant

Ovid (Medline) search

Search terms	Results
"Rifaximin" AND "hospital$"	2 observational studies, both US: • Leevy and Phillips, 2007[16] • Neff et al[15]

Internet searching

Google search terms	Results
“clinical audit hepatic encephalopathy”	No relevant hits
“clinical audit rifaximin”	No relevant hits
“rifaximin real world”	No relevant hits
“rifaximin hospital admission”	No relevant hits

Appendix 2. Study characteristics, participant characteristics and treatment received in the 4 RWD audits included in the meta-analysis in the further submission and [redacted]

Study (location)	**Goel et al, 2014[10] (Bolton)** **Abstract only**	**Orr et al, 2013[9] (New castle)** **Abstract only**	**Roche et al, 2013[7] (Dundee)** **Abstract only**	**Valliani et al, 2012[8] (Bristol)** **Abstract only**	[redacted]
Number who entered study / Attrition and reasons / Number in final analysis	N = 30 5 died (within 6 months of commencing rifaximin-α), 1 discontinued. n = 24	N = 64 8 discontinued, 23 died. 33 remained, but complete data only available for 25. n = 25 (survivors)	N = 16 Assume n = 16	N = 16 3 died on same admission as when received rifaximin-α and 3 died within 6 months of starting rifaximin-α n = 4 at 12 months	[redacted]
HE / liver disease	Recurrent HE 83% alcohol-related liver disease; 10% NASH and 7% Hepatitis C	53% ALD	"Long-term treatment for HE" Alcoholic liver disease (n = 7), non-alcoholic steatoheptitis (n = 6), hepatitis C (n = 1), autoimmune hepatitis (n = 1), iagtrogenic post splenic artery rupture repair (n = 1)	HE "refactory to conservative measures" Child Pugh class B: n = 5 Child Pugh class C: N = 11	[redacted]

Age	Median age 64 (IQR 51-67)	Age not reported	Mean age 61 (range 42 to 73) years	Mean age 59.1	[redacted]
MELD score	Median MELD score 15.5 (IQR 13.5-21)	Non-survivors: Mean MELD 19.0 Survivors: Mean MELD 13.0 P < 0.05	Not reported	Not reported	[redacted]
Whether study measured HE-related or all cause hospital admissions	Not reported	Not reported	Not reported	HE admissions	[redacted]
Treatment received before rifaximin-α	Not reported	Not reported	Not reported	"Conservative measures"	[redacted]
Design details and treatment received when rifaxmin-α initiated	Compared admissions and bed days for 6 months before vs 6 months after taking Rifaximin-α. Dose and duration of treatment not reported. All prescribed lactulose	Compared emergency admissions and bed days for 1 year before vs one year after taking Rifaximin-α. Dose and duration of treatment not reported. 40 (63%) took concomitant lactulose	Before and after – exact period not specified. Across patients combined months on Rifaximin-α were 233 vs 203 off.	Compared 12 months pre-rifaximin-α to 6 and 12 months post-rifaximin-α. Rifaximin-α dose of 1.14 grams/day in divided doses. 12 patients had received rifaximin-α for at least 6 months	[redacted] [redacted]

Study period	Period 11/2011 - 05/2013	Period 01/2011 - 12/2011	Period 01/2011 - 12/2011	Patients prescribed rifaximin-α between October 2007 – August 2010	[redacted]
Sponsor	Not reported	Not reported	Not reported	Not reported	[redacted]

Appendix 3: Comparison of length of inpatient stay (bed days per person) data reported in original sources and different parts of the further submission

Study, observation period	Data source	Average days measure (variance) (unless stated)	n in final analysis (unless stated)	Before rifaximin-α, bed days per person (unless stated)	After rifaximin-α, bed days per person (unless stated)	p-value	Difference (average reduction in bed days, per person - unless stated)	% reduction
Data included in meta-analysis								
Goel et al, 2014[10] (Bolton), 6 months	Original source (abstract only)[10]	Median (IQR, range)	24	27.5 (16.0-35.3, 2-129) (not annualised) per admission	2.5 (0-23.5, 0-55) (not annualised) per admission	P < 0.05	25 (not annualised) per admission	90.9 (not annualised)
	Meta-analysis data (further submission Table 7)	**Mean (SD) – annualised**	**24**	**92.0 (SD 72.20)[1]**	**30.0 (SD 31.79)[1]**	**NR**	**62**	**67.4**
	Preliminary descriptive analysis	Unclear if median or mean – stated annualised, but probably in error	24	27.5	2.5	NR	25	90.9
	Appendix C of further submission	Median (IQR, range)	24	27.5 (16.0-35.3, 2-129) bed days	2.5 (0-23.5, 0-55) bed days	P < 0.05	25 (not annualised)	90.9 (not annualised)
Orr et al, 2013[9] (Newcastle), 12 months Emergency hospital	Original source[9] (abstract only)	Mean	25	30.2 per person per year	9.8 per person per year	P < 0.05	20.4 per person per year	67.5

admissions								
	Meta-analysis data (further submission Table 7)	**Mean (SD)**	**27**	**28.4 (26.30)**	**9.4 (SD 14.70)**	**NR**	**19**	**66.9**
	Preliminary descriptive analysis	Mean (SD)	Stated 64 (which is number who entered study)	28.4	9.4	NR	19	66.9
	Appendix C of further submission	Mean (SD)	27	28.4 (26.3) per person per year	9.4 (14.7) per person per year	P < 0.05	19	66.9
Roche et al, 2013[7] (Dundee), variable	Original source[7] (abstract only)	Unclear if median or mean (range)	NR, 16 entered study	7.6 (1-58) (not annualised) per admission	4.9 (1-26) (not annualised) per admission	P < 0.05	2.7 (not annualised) per admission	35.5 (not annualised)
	Meta-analysis data (further submission Table 7)	**Mean (SD) - annualised**	**16**	**16.2 (17.59)**	**3.5 (17.59)**	**NR**	**12.7**	**78.4**
	Preliminary descriptive analysis	Mean (SD) - annualised	16	13.8	4.6	NR	9.1	66.4
	Appendix C of further submission	Unclear if mean or median (range)	16	7.6 (1.58) (not annualised), average length of stay	4.9 (1-26) (not annualised), average length of stay	P < 0.05	2.7 (not annualised)	35.5 (not annualised)
Valliani et al, 2012[8] (Bristol), 12 months	Original source[8] (abstract only)	Mean	Pre-rifaximin-α: 12 6 months: 6 12 months: 4	14.6 per admission ERG calculations	10.6 at 6 months; per admission 12.4 at 12			

				: 34.0[2] per person per year	months, per admission ERG calculations: 15.5[3] per person per year			
	Meta-analysis data (further submission Table 7)	**Mean (SD)**	**12**	**34.0 (14.94) (N = 12)**	**15.5 (14.94) (N = 4)**	**NR**	**18.5**	**54.4**
	Preliminary descriptive analysis	Unclear if median or mean	16	33.6	13.8	NR	19.8	Reported as 59.0 (ERG calculated 58.9)
	Appendix C of further submission	Unclear if median or mean	Pre-rifaximin-α: 12 6 months: 6 12 months: 4	2.83 (the original source shows that this is per person per month)	1.78 (6 months) 1.29 (12 months) (The original source shows that these data are per person per month)	NR	1.05 (6 months) 1.54 (12 months)	37.1 (6 months) 54.4 (12 months)
References excluded from meta-analysis								
Patel et al 2014,[11] 'Kings' combined Multi-centre data' of 4 hospitals (Kings,	Original source[11] (abstract only)	Unclear if median or mean	N = 170 (entered study) Bed days data: n = 73	23 ± 25 per admission	NR	-	-	-

Newcastle, Portsmouth, Liverpool), 3 months								
	Appendix C of further submission	Unclear if median or mean	N = 170 (entered study) Bed days data: n = 73	23 ± 25 per admission	NR	-	-	-
Preedy et al, 2014[12] (Portsmouth), 6 months	Original source[12] (poster only)	Total bed days	3 months: 26 (62%) 6 months: 16 (38%) 12 months: 12 (26%)	233 total	3 months: 28 6 months: 143 12 months: 158	NR	90 at 6 months Average 5.6 per person	6 months: 38.6% (of total)
	Appendix C of further submission	Total bed days (for cohort)	3 months: 26 6 months: 16 12 months: 12	233 (9.3 per admission[4])	3 months: 28 (14 per admission[4]) 6 months: 143 (13 per admission[4]) 12 months: 158 (7.9 per admission[4])	-	6 months: 90 (total)	6 months: 38.6% (of total)

Data in shaded cells were calculated by the ERG. Data used in meta-analysis is highlighted in bold. NR, not reported; SD, standard deviation; HE, hepatic encephalopathy. [1]Company derived these data by transforming the 6 month medians and ranges reported in the original source to means and SDs and then annualising the data. The ERG has replicated the transformation of the 6 month data and it appears to be accurate. However, it is unclear if the bed days data used in the meta-analysis is per patient per year or per patient per year *per admission*, because the original source data is bed days per admission and it is unclear if this was transformed to per patient per year data. [2]Calculated by ERG (2.33 admissions per patient pre rifaximin-α * 14.6 bed days pre-rifaximin-α per admission). [3]Calculated by ERG (1.25 admissions per patient post rifaximin * 12.4 bed days post-rifaximin-α per admission). [4]Calculated by the ERG (total number of bed days divided by number of admissions as reported in Appendix C).