The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy

A critique of the submission from Norgine

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Title

The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy

Source of funding

This report was commissioned by the NIHR HTA Programme as project number 11/38/01

Produced by

Matrix
Peninsula Technology Assessment Group (PenTAG)

Although Matrix are primarily responsible for the work in this report, PenTAG retains responsibility for the standard of the report and the quality of the advice that it contains.

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Acknowledgements

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Declaration of competing interest of the authors

None

Rider of responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Bacelar M, Bertranou E, Cooper C, Hyde C, Venkatachalam, M. The clinical and cost-effectiveness of rifaximin for maintaining remission from episodes of hepatic encephalopathy. Single Technology Appraisal NIHR HTA Programme (11/38/01), Matrix and Peninsula Technology Assessment Group, 2013.

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Date completed

April 2013

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1.0 Summary

Text cited directly from the submission by Norgine (hereafter referred to as 'the submission') is presented in italic and cross referenced.

1.1 Scope of the submission

The submission from Norgine considered the use of rifaximin-α (Targaxan®) for the reduction in the recurrence of episodes of overt hepatic encephalopathy (HE) in patients 18 years of age and older. In the study used for the submission, 91.3% of the patients were using concomitant lactulose. The comparator used was placebo with concomitant lactulose.

The clinical effectiveness outcomes considered were: frequency of recurrent acute episodes of HE and time to next episode; disease progression to more severe grades of HE; frequency of hospitalisation and time until next hospitalisation; mortality; adverse effects of treatment; and health related quality of life.

The outcome for the economic analysis was the incremental cost per quality-adjusted life year (ICER). The time horizon for the economic analysis was five years and costs were considered from an NHS and personal social services perspective.

Subgroup analyses were presented in the economic analysis. The following patient groups were considered: patients receiving concomitant lactulose in both arms of the model (91.3% of the ITT population in the study used for the submission) and patients not receiving lactulose (8.7%, respectively). Both subgroups were a non pre-planned subgroup analysis in the clinical trial.

1.2 Summary of submitted clinical effectiveness evidence

The submission from Norgine included two studies: a good quality RCT, RFHE3001, n=299 (Bass et al, 2010; CSR RFHE3001) and a non-RCT, RFHE3002, n=322 (CSR RFHE3002).

RFHE3001 was a Phase III randomised, double-blind, placebo-controlled study conducted over a 6 month period. The main objective of the study was to evaluate the efficacy of rifaximin (550 mg twice a day) compared with placebo, in patients who were in remission from recurrent, overt, episodic HE resulting from chronic liver disease. 140 patients were randomised to the rifaximin arm and 159 patients were randomly allocated to the placebo arm. A large proportion of patients in the rifaximin arm were treated with rifaximin and lactulose combined, while patients in the placebo arm were treated with lactulose alone.

RFHE3002 was an open-label Phase III study. The main objective of the study was to provide long-term evaluation of the safety and tolerability of rifaximin. Patients who successfully completed the Phase III RCT (RFHE3001) were eligible to participate in study RFHE3002 in addition to new patients.

Superseded - see erratum

The manufacturer's submission summarised the identified benefits as:

- Rifaximin 550 mg twice a day plus lactulose significantly reduced ($p<0.001$) the relative risk of recurrence of overt HE episodes by 58% (hazard ratio 0.42, 95% confidence interval (CI), 0.28 to 0.64) vs. placebo plus lactulose over 6 months.
- Rifaximin 550 mg twice a day plus lactulose significantly reduced ($p=0.01$) the relative risk of hospitalisation involving HE by 50% (hazard ratio 0.50, 95% CI, 0.29 to 0.87) vs. placebo plus lactulose over 6 months.
- Norgine indicated that the incidence and seriousness of adverse events reported during the study was similar between the rifaximin and placebo groups. However they did not present relative risks and risk difference and associated 95% confidence intervals for each adverse event, which would have provided a stronger case for their decision of not costing adverse events.
- RFHE3002 showed that long term treatment over 24 months with rifaximin 550 mg twice a day plus lactulose provided continued protection from HE and reduced the hospitalisation rate.

Norgine considered that the mortality data from trial RFHE3001 was not mature enough to capture the drug overall impact on survival. However the model submitted captures the effect on mortality of rifaximin vs. placebo by reducing the recurrence of HE events, and the reduced mortality rate associated with such reduction is a major source of QALYs gained.

1.3 Summary of submitted cost effectiveness evidence

Norgine developed a state transition Markov approach to model the cost-utility of rifaximin concomitant with lactulose compared to placebo concomitant with lactulose. The model has three health states: remission; overt (capturing the primary outcome of the analysis which is time to first breakthrough HE episode); and death.

Norgine's base case analysis produced an ICER of £23,186 per QALY. Their one-way sensitivity analyses produced a range of ICERs from £15,032 per QALY to £28,844 per QALY.

The subgroup analysis estimated an ICER of £25,785 per QALY for patients receiving concomitant lactulose in both arms of the model (91.3% of the ITT population in the study used for the submission) and an ICER of £36,254 per QALY for patients not receiving lactulose (8.7% of the ITT population). Particular caution should be taken when interpreting these results, especially due to the small sample size in the second group and the potential large variability of the estimate.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

Clinical effectiveness

- It is likely that the clinical systematic review of the literature undertaken by Norgine contains all the relevant studies.
- The RCT is of high quality.

Cost-effectiveness

- The approach taken to modelling is reasonable.
- The sources and justification of estimates were also generally reasonable.

1.4.2 Weaknesses

The evidence is based on only one completed and published RCT. The follow-up study is an unpublished long-term evaluation of the safety and tolerability of rifaximin, and does not provide treatment effect data.

In their economic evaluation, Norgine presented some minor errors. After correcting for all errors, the final ICER is £22,298 per QALY.

A number of omissions were made in the sensitivity analysis. In particular, the lognormal constant parameter used to model time to first HE episode in the placebo arm and the exponential regression parameters used to model the subsequent HE episodes, were not included in both one-way and probabilistic sensitivity analyses.

1.5 Key issues

The submitted evidence reflects the decision problem adequately even though it parted from NICE original scope, especially in terms of population and comparators covered, namely:

- **Population**. The analysis refers to adults with chronic liver disease who have had prior episodes of overt HE and are currently in remission. Patients with more severe liver disease (MELD score ≥25) were excluded from the analysis. Therefore, the indication and submission do not cover patients with HE caused by an acute liver insult and patients with more severe liver disease.
- **Intervention**. Although in the scope the intervention was specified as rifaximin, in the study used for the submission 91.3% of the patients were using concomitant lactulose. As indicated previously, for patients not receiving lactulose (8.7%) the ICER is £36,254 per QALY and due to the small sample size it is potentially subject to large variability. Therefore, if the indication of rifaximin is meant for patients taking rifaximin alone, then

- the economic model developed by Norgine for this submission is not sufficient to inform the overall costs and benefits of the drug.
- **Comparators**. The comparator used in the analysis is placebo plus concomitant lactulose. Neomycin and neomycin with lactulose were not used as comparators.

Finally, as per consultation with our expert clinical advisor, the underlying assumption of a constant probability of subsequent HE episodes over time is not necessarily reflective of reality. [redacted]

Although Norgine considered that the mortality data from trial RFHE3001 was not mature enough to capture the drug overall impact on survival, the model submitted captures the effect on mortality of rifaximin vs. placebo through the reduction in the recurrence of HE events. The reduced mortality rate associated with such reduction is a major source of QALYs gained.

Superseded - see erratum

2.0 Background

2.1 Critique of manufacturer's description of underlying health problem

In Sections 2.1 to 2.3 (Submission pp.12-17) Norgine describes the underlying health problem. They provide a detailed summary of the characteristics and progression of HE. Incidence or prevalence of HE data is reported as not found and the number of patients with recurrent episodes of HE in England and Wales remains uncertain. However, based on the prevalence of cirrhosis it was estimated that about 23,600 patients may have subclinical or mild HE, and 5,500-9,500 may progress to a more severe form of the disease.

Similarly, information on life expectancy of patients with recurrent episodes of HE in England and Wales is reported as not found. One study (Bustamente et al, 1999) reported that 42% of patients who experienced an episode of HE had survived at one-year follow-up and 23% at 3 years.

2.2 Critique of manufacturer's overview of current pathway of care and service provision

In Sections 2.5 to 2.7 (Submission pp.17-21) Norgine states that there are no recognised diagnostic pathways or treatment guidelines for HE. However they provide a summary of the typical care pathway in England and Wales based on information provided by UK liver specialists. Specialists highlighted that there is variability in the provision of care for patients with HE and there is inequity in the provision of or access to rifaximin in the management of the condition.

As indicated by Norgine (Submission p.23) lactulose is the current standard of care and is routinely used in clinical practice for management of HE.

Neomycin would appear not to be routinely used in clinical practice in the prevention of recurrence of in patients in remission. Based on neomycin usage in Primary Care in England in 2011 (as sourced from Prescription Cost Analysis via the NHS Information Centre) there were only 29 prescriptions of Neomycin Tablets 500mg issued in the year 2011, and 2,320 tablets used. Furthermore, as the data source does not specify an indication we believe that this usage is likely to be across a number of different indications. Norgine considers that overall neomycin usage is minimal and it should therefore not be included as a comparator. This was confirmed by UK liver specialists.

However, our clinical advisor indicated that although in some patients neomycin is not as well tolerated as rifaximin, it is sometimes used in clinical practice (especially in patients that will not undergo liver transplant).

3.0 Critique of manufacturer's definition of decision problem

3.1 Population

The population considered by the submission is adults with chronic liver disease who have had prior episodes of overt hepatic encephalopathy (HE) and are currently in remission.

This is to some extent different from the population defined in the NICE Scope[1] defined as adults who have had prior episodes of HE and are currently in remission. Therefore, the indication and submission do not cover patients with HE caused by an acute liver insult.

In addition, the submission excludes patients with more severe liver disease (MELD score ≥25).

3.2 Intervention

The intervention under assessment is rifaximin-α (Targaxan®). UK authorisation was gained in January 2013. Rifaximin-α[2] is indicated for the reduction in the recurrence of episodes of overt HE in patients 18 years of age and older. In the study used for the submission, 91% of the patients were using concomitant lactulose. Our clinical expert agrees that the use of concomitant lactulose represents current practice in the UK.

The rifaximin dose is 550mg twice daily for 6 months. Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction (Submission p.10).

3.3 Comparators

The comparator used was placebo plus concomitant lactulose. This differs from the comparators specified in the scope which included: lactulose, neomycin, and neomycin with lactulose.

The submission provides three reasons for the exclusion of neomycin as comparator (Submission p.27). These are outlined in Table 1, along with comments based on clinical expert opinion which suggests that the exclusion of neomycin as a comparator raises some concerns.

Superseded - see erratum

[1] Referred to as 'the scope' in the remainder of this report.
[2] Referred to as 'rifaximin' in the remainder of this report.

Table 1. Reasons for excluding neomycin as comparator

Reason for excluding neomycin as comparator	Critique based on clinical expert opinion
Neomycin is not licensed for the indication.	Neomycin is an antibiotic that works through the same process as rifaximin. Although in some patients neomycin is not as well tolerated as rifaximin, it is sometimes used in clinical practice (especially in patients that will not undergo liver transplant).
Neomycin is not commonly used in clinical practice for long-term prevention of HE recurrence. The neomycin summary of product characteristics (SPC) contains warnings against long-term use.	There are no equivalent studies assessing the long-term use of rifaximin and its side effects. Therefore similar warnings against long-term use of rifaximin cannot be ruled out.
There is no evidence for the efficacy of neomycin or neomycin and lactulose in combination in this indication.	A study (Miglio et al, 1997) comparing the effectiveness of rifaximin and neomycin was identified. Norgine considered inappropriate to use this study to inform a comparison of neomycin with rifaximin due to differences in the patient population, treatment regimens and outcomes used in their main effectiveness study (RFHE3001). As stated previously however, neomycin is sometimes is used in patients with similar characteristics as those that would be indicated rifaximin.

3.4 Outputs

The outcomes considered in the submission include:

- Disease progression to more severe grade of HE
- Frequency of hospitalisation, and time until next hospitalisation
- Frequency of recurrent acute episodes of HE and time to next episode
- Mortality
- Adverse effects of treatment
- Health related quality of life

Cost-effectiveness was expressed in terms of incremental cost per quality-adjusted life year.

3.5 Time frame

The time horizon for the economic analysis was 5 years. Our clinical expert agrees that this is an appropriate time frame to capture the incremental costs and benefits of the intervention, with a majority of HE patients expected to have died within the time frame. Those alive after 5 years are likely to be patients with stable liver disease.

Superseded - see erratum

4.0 Clinical effectiveness

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate

- Clinical effectiveness

Two searches were performed for clinical effectiveness.

First search - submission

Bibliographic searching was initially conducted on May 29th 2012 in the following databases:

- MEDLINE (R) In-Process & Other Non-Indexed Citations and OVID MEDLINE(R) 1946 to present
- EMBASE via OVID 1980 to 2010 week 36
- The Cochrane Library via OVID (CENTRAL, CDSR, DARE and HTA) data parameters not provided

The main (first) bibliographic search strategy combined population terms (for hepatic encephalopathy/ liver cirrhosis) and intervention terms (rifaximin, lactulose and neomycin). These were combined with a search filter to randomised trials. A standard limit to remove non-trial material was employed. No further limits (such as a limit to human only populations) were used. The search strategies and resources used were appropriate to the task.

In this search, the EMBASE search is recorded as being run 1980 to 2010 Week 36. Norgine indicated in clarification (appendix A Response to D1) that the EMBASE search was updated on December 12th to run 1988 to 2012 week 49. This was done using the second search strategy (discussed below).

The following supplementary search methods were used in the first effectiveness search:

- Hand-searching of reference lists of included RCTs;
- Hand-searching of RCTs included in recent, relevant systematic review publications; and,
- Hand-searching of conference publications to identify any recent RCTs for which there are currently no full publications.

The following conference proceedings were searched:

- European Association of the Study of the Liver (EASL)
- The international Liver Congress

- Monothematic Conference
- International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN)
- United European Gastroenterology Week (UEGW)

The following trials registries and web-sites were searched to identify on-going, unpublished studies.

- WHO International Clinical Trials Registry Platform (ICTRP)
- Clinicaltrials.gov
- NCI Clinical Trial database
- ISRCTN Register
- UK Clinical Trials Gateway
- metaRegister (mRCT) of controlled Trials

Norgine also searched their manufactures database for unpublished studies.

Second search - clarification

In clarification, Norgine confirmed additional searches had been run on December 12th/13th 2012 with the view of updating the literature. This used a different, less sensitive, search strategy to the first search. It combined terms for hepatic encephalopathy (but not terms for liver cirrhosis, as previously) with intervention terms (rifaximin- α, lactulose and Neomycin). A limit to randomised trials was used and this search was limited to human only populations and to English language studies.

This search was performed in the same databases as the first effectiveness search. This search also searched the following annual meetings (in addition to those mentioned above but with different time-frames) for the following organizations 2011/2012:

- United European Gastroenterology (UEG)
- American Gastroenterological Association (AGA)
- American Association for the Study of Liver Diseases (AASLD)

In principle, this search reflects the core criteria of the submission but does not strictly mirror the first search so cannot be seen as a full update. As such, it is possible that items could have been missed between the two searches however, as they overlap one another, we mention this only to note the second search is limited by population and language.

We are concerned by one issue in the second search. Norgine spelt out the primary intervention differently in this second search: here they used rifaximin-α compared to the main search which used Rifaximin. Whilst the former is, strictly speaking, the name of the intervention, for sensitivity, it would have been advisable to search on both expressions. In testing the search, the ERG had to amend the December 2012 effectiveness searches to allow for this.

In cross-checking this, on these two terms alone, the Medline and Embase searches returned identical results (between ("Rifaximin-α".ti,ab.) / (Rifaximin).ti,ab.) but the Cochrane searches record a nil result on "Rifaximin-α" and missed records where the following line was used:

#5	Rifaximin-α or rifamycin or Xifaxan or refero or targaxan or tixteller or xifaxanta or redactiv or 80621-81-4 or 88747-56-2	182

(Appendix A: Updated Effectiveness Search (Response to D1))

Had the search term 'Rifaximin' (alone or with both expressions) been used, this would not have happened.

- Adverse effects

No separate searches to locate adverse event literature were conducted by Norgine.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

Studies were included if they referred to adults who have had prior acute episodes of HE (grade II to IV), types A, B, and C. Studies were excluded if subjects were <18 years of age and/or subjects had not had prior acute episodes of HE.

Studies were included if they intervention assessed was rifaximin, neomycin or lactulose.

Outcomes of interest were:

- Disease progression to more severe grade of HE
- Frequency of hospitalisation
- Frequency and severity of recurrent acute episodes of HE
- Mortality
- Adverse effects of treatment
- Health-related quality of life
- Rate of liver transplantation

Studies not investigating efficacy, safety or quality of life were excluded.

Studies included were limited to Phase II or III randomised controlled trials. Both double-blind and open-label RTCs were included. Any studies that were not randomised controlled studies were excluded.

Abstracts and publications not available in English were excluded.

These inclusion and exclusion criteria are appropriate. However, the submission does not explain the process used in study selection (e.g. How many people were involved in reviewing abstracts and titles? How were differences in opinion resolved?).

4.1.3 Studies included and excluded

The search strategy identified 322 potentially non-duplicate publications resulting in 11 studies (reported in 18 publications) that met the inclusion criteria. Reasons for excluding publications were generally well reported. The breakdown of studies by intervention/comparator was as follows:

- Rifaximin studies (n=3): Bass et al (2010); Loguerico et al (2003); Paik et al (2005).
- Neomycin (n=0).
- Lactulose studies (n=8): Bresci et al (1993); Elkington et al (1969); Heredia et al (1988); Loguerico et al (1995); Poo et al (2006), Raza et al (2004); Sharma et al (2009); Takuma et al (2010).

Lactulose studies were not used further in the submission.

Of the three rifaximin studies, two were subsequently excluded from the submission. *Loguerico et al (2003) involved pulse/cyclical treatment with rifaximin at a different dose/regimen to the UK licensed indication for rifaximin. Paik et al (2005) involved treatment with rifaximin at a different dose/regimen to the UK licensed indication for rifaximin in a Korean population* (Submission p.31).

Bass et al (2010) provides results of a Phase III RCT (RFHE3001) for rifaximin compared to placebo. In this randomised, double-blind, placebo-controlled trial, 299 patients who were in remission from recurrent hepatic encephalopathy resulting from chronic liver disease were randomly assigned to receive either rifaximin, at a dose of 550 mg twice daily (140 patients), or placebo (159 patients) for 6 months. The primary efficacy end point was the time to the first breakthrough episode of hepatic encephalopathy.

*A separate review of the unpublished data from the manufacturer database was also undertaken to identify any relevant unpublished data in the population of interest (i.e. adults who have had prior acute episodes of HE). One further study was identified, an open-label Phase III study (RFHE3002) which provides long-term evaluation of the safety and tolerability of rifaximin. Patient who successfully completed the pivotal Phase III RCT (RFHE3001) were eligible to participate in study RFHE3002 in addition to new patient*s (Submission p.33).

Bass et al (2010) and the Clinical Study Reports (CSRs) for RFHE3001 and RFHE3002 are the main source of information for this submission.

4.1.4 Details of any relevant studies that were not included in the submission

The ERG identified one RCT study (Miglio et al, 1997) of the efficacy of rifaximin compared to neomycin in the treatment of HE. In clarification Norgine reported that they had also identified

Miglio et al (1997) in their clinical systematic review. However, the study had been subsequently excluded for the following reasons (Clarification document provided by Norgine upon the ERG request):

- *Patient population*
    - *The patient population was chronic HE rather than patients with HE who had been in remission and therefore did not match the patient population in the decision problem.*
    - *Patients in the study had a Conn score of 1 or 2. This meant that some patients were not in remission when recruited into the trial and therefore did not match the patient population in the decision problem.*
    - *No detail on prior episodes reported. This was stated as an exclusion criterion in the systematic review so that the patient population in any identified studies would be similar enough to include in a meta-analysis or indirect comparison.*
- *Treatments*
    - *Both treatments (rifaximin and neomycin) were given for 14 consecutive days of every month. This did not represent the licensed dose for rifaximin nor how rifaximin would be used in clinical practice. Consequently, a comparison between the two studies (Bass et al, 2010 and Miglio et al, 1997) would have been inappropriate.*
- *Outcomes*
    - *Miglio et al (1997) did not report either of the following outcomes:*
        - *time to first breakthrough episode of hepatic encephalopathy or time to first hospitalisation involving hepatic encephalopathy (the primary and secondary endpoints in Bass et al 2010, respectively).*
    - *The clinical and safety assessments in Miglio et al (1997) were outlined as follows:*
        - *"The treatment was considered effective when an improvement of at least one grade of HE was detected. Adverse events and their relationship to treatment were monitored during all of the study period."*
    - *The results reported were as follows:*
        - *In all patients a clear-cut progressive reduction in HE grade, with no difference between the two treatment groups, was observed. In particular, the improvement in HE was already statistically significant after 30 days ($p<0.001$ for each group).*
        - *No further information on grade of HE over time was reported.*
    - *The differences in outcomes between Miglio et al (1997) and Bass et al (2010) meant that inclusion of this study in comparing rifaximin with neomycin was completely inappropriate with respect to statistical analysis.*

Due to differences in the patient population, treatment regimens and outcomes stated above, Norgine considered inappropriate to use this study to inform a comparison of neomycin with rifaximin. We acknowledge these differences and the justification provided by Norgine to

exclude Miglio et al (1997). The study has been used to inform a scenario analysis just for illustrative purposes.

4.1.5 Description and critique of manufacturer approach to validity assessment

In this section the two main studies used in Norgine analysis are assessed for their validity. RFHE3001 (RCT) and RFHE3002 (follow-up study) were initially assessed by Norgine. We present our comments alongside their assessment.

Table 2 provides the quality assessment of study RFHE3001.

Table 2. Clinical appraisal of relevant RCTs

Assessment question	Norgine response	ERG comments
Was randomisation carried out appropriately?	Yes	Yes *Patients were randomly assigned on Day 0 (Visit 2) to receive rifaximin 550 mg BID or placebo BID in a 1:1 ratio.*(Submission p.36) In response to request to clarification Norgine indicated that: • *A total of 299 subjects were randomised to receive placebo (159 subjects) or rifaximin (140 subjects) in this study between December 2005 and August 2008. The United States and Canada analysis region included 219 subjects and 80 subjects were randomised and treated in Russia.* • *The randomisation code for this study included a block size of 4 and was stratified by site.* • *Because the number of subjects at each site was not a multiple of 4, there was some imbalance between treatment groups (159 subjects in the placebo group and 140 subjects in the rifaximin group).*
Was the concealment of treatment allocation adequate?	Yes	Yes *Patients, investigators and other personnel participating in the trial were blinded to the study treatments by their identical appearance and labelling. The investigator was permitted to unblind a patient's treatment assignment only in an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the patient.* (Submission p.36)

Assessment question	Norgine response	ERG comments
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes *The median age of patients was 56 (ranging from 21 to 82) with 19.4% of patients being over the age of 65. Most patients were white (86%) and male (60.9%). The relative distributions of patients by demographic characteristics were comparable between treatment groups in the ITT population.* (Submission p.40) There was a slight overrepresentation of males in the placebo arm (67%) when compared with the rifaximin arm (54%) *No. of HE episodes in the past 6 months were 2 in 69.3% with rifaximin group and 69.8% with comparator group; Conn score during most recent HE episode before study was 2 in 82.1% with rifaximin and 81.8% with comparator group, Conn score of 3 or 4 was in 16.4% with rifaximin and comparator group alike.* (Submission p.180) Duration of current remission before trial was somewhat longer for patients in the placebo arm (158 days with mean of 73 days and standard deviation of 47.7) when compared with patients in the rifaximin arm (139 days with a mean of 69 days and standard deviation of 51.3)
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes. *Patients, investigators and other personnel participating in the trial were blinded to the study treatments by their identical appearance and labelling. The investigator was permitted to unblind a patient's treatment assignment only in an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the patient.* (Submission p.36)
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No From the 140 patients in the rifaximin arm, 52 patients (37%) discontinued the study drug. Out of these 52 patients, 54% had as primary reason breakthrough HE while 46% had as primary reason a non breakthrough event (e.g. adverse event, death, etc). From the 159 patients in the placebo arm, 93 patients (58%) discontinued the study drug. Out of these patients, 74% had as primary reason breakthrough HE while the remaining 26% had other reasons. The requested withdrawal was similar in both arms (4.3% and 5.7% in the rifaximin and placebo arm respectively).

Assessment question	Norgine response	ERG comments
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No *All measured outcomes were reported.* (Submission p.181)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes/no information available. Efficacy and secondary outcomes in the analysis were calculated on an intention-to-treat basis. All randomized patients who received at least one dose of study drug and provided at least 1 post-baseline safety assessment were included in the safety population. The submission report did not provide any detail on censoring method nor or missing data. However, we looked into the clinical report (Salix, Clinical study report RFHE3001) and found a description regarding these points: • Subjects who did not experience a breakthrough overt HE were censored at the time of contact or death, whichever was earlier. • Subjects who terminated earlier for reasons other than breakthrough overt HE were contacted 6 months from date of randomization to determine if they had experienced a HE episode or other outcome.

Table 3 reports the quality assessment strategy of non-RCT evidence (RFHE3002 study). The criteria used are outlined in Chamber et al (2009).

Table 3. Critical appraisal of non-RCT evidence

Assessment question	Norgine response	ERG comments
Eligibility criteria adequately reported?	Yes	Yes *All eligible patients had a history of HE, a Conn score of 0 to 2 at enrolment, and either successfully participated in the previous HE study with rifaximin (RFHE3001), or were new patients enrolled with ≥ 1 verifiable episode of HE within 12 months prior to screening. Patients who had participated in RFHE3001 and had experienced a HE episode or associated symptoms were only eligible for this study if the investigator and patient did not perceive study medication as a possible cause of the HE episode/symptoms.* *Inclusion and exclusion criteria were otherwise those already described for study RFHE3001.* (Submission p.63)

Assessment question	Norgine response	ERG comments
Study population representative of a normal population?	Yes	Yes Study population included patients from RFHE3001 study (70 patients) as well as new participants (252). The characteristics of the population were considered to be representative of UK population with liver disease.
An appropriate measure of variability reported?	Yes	Yes
Loss to follow-up reported or explained?	Yes	Yes [redacted]
At least 90% included at baseline followed-up?	Yes	Yes
Were patients recruited prospectively?	Yes	Yes Study population included patients that concluded RFHE3001 study as well as new participants.
Were patients recruited consecutively?	Yes	Yes Patients meeting the inclusion criteria were admitted into the study during a 7 day screening period.
Did the study report relevant prognostic factors?	Yes	Yes. [redacted]
Quality score[3]	Good	Good

4.1.6 Description and critique of manufacturers outcome selection

- RFHE3001

The primary efficacy endpoint of RFHE3001 trial was time to first breakthrough overt HE episode. An overt HE episode was defined as an increase in the Conn score to 2 or above (i.e. 0 or 1 to ≥2) or an increase in both the Conn and asterixis score of 1 grade for those patients who entered the trial with a Conn score of 0. All patients were in remission at baseline.

[3] Good, if the answer is ‘‘yes’’ to all of criteria 1-8; satisfactory, if the answer is ‘‘yes’’ to criteria 2, 4-7; poor, if the answer is not ‘‘yes’’ to one or more of the criteria listed for ‘‘satisfactory.’’

Other outcomes were also assessed in RFHE3001 study. The five key secondary outcomes included in the study are reported below:

- *Time to first hospitalization due to an HE event*
- *Time to any increase from baseline in Conn score*
- *Time to any increase from baseline in asterixis grade*
- *Mean change from baseline in fatigue domain score on the Chronic Liver Questionnaire Disease (CLDQ) at end of treatment*
- *Mean change from baseline in venous ammonia concentration at end of treatment*

Other secondary outcomes were also reported by Norgine:

- *Time to diagnosis of spontaneous bacterial peritonitis*
- *Mean change from baseline in critical flicker frequency values at each post-baseline assessment and at end of treatment*
- *The numbers and proportions of patients in each level of change from baseline in Conn scores at each post-baseline assessment and at end of treatment.*
- *The numbers and proportions of patients in each level of change from baseline in asterixis grades at each post-baseline assessment and at end of treatment.*
- *Mean change from baseline in Epworth Sleepiness Scale (ESS) total score at each post-baseline assessment and at end of treatment.*
- *Proportion of patients who had an ESS total score ≥10 at each post-baseline assessment and at end of treatment*
- *Mean change from baseline in SF-36 QoL scores at each post-baseline assessment and at end of treatment*
- *Average daily lactulose usage (cup/day, 1 cup = 15 mL)*

(Submission pp.44-54)

- ### RFHE3002

The follow-up study RFHE3002 reported the following main outcomes*:*

- Change from baseline in Conn scores over time
- Changes from baseline in asterixis grades over time

The following safety endpoints were evaluated:

- Incidence of treatment-emergent adverse events, grouped by body system, relationship to study medication, and severity.
- Change from baseline in clinical laboratory parameters at Months 1 and 3, and every 3 months thereafter until EOT.
- Changes from baseline in vital sign measurements at Months 1 and 3, and every 3months thereafter until EOT.

The manufacturer's choice of outcomes is considered to be appropriate. It is in accordance with both RFHE3001 and RFHE3002 study outcomes which are also in line with the outcome measures specified in the final scope.

4.1.7 Description and critique of the statistical approach used

- RFHE3001: Planned statistical analysis

Two study populations were included in the analysis:

- The intention-to-treat population (ITT), including all randomised subjects who received at least 1 dose of rifaximin.
- The safety population, also including all randomised subjects who received at least 1 dose of rifaximin and who have provided at least 1 post-baseline safety assessment.

The ITT population was used for the efficacy analyses.

For the analysis of the primary efficacy endpoint, time to first overt HE episode was compared between rifaximin and placebo groups, adjusting for analysis region. This was done using a Cox proportional hazards model (with Log rank test stratified by analysis region), with a two-sided test and significance level of 0.05 under the proportional hazards assumption. If the assumption was violated, an alternative model, for example Cox models with non-proportional hazards, was to be used instead. Furthermore, Kaplan-Meier time-to-event methods were used to estimate the proportions of subjects experiencing a HE episode on days 28, 56, 84, 140 and 168 for each treatment group. All time-to-event outcomes were analysed in the same fashion.

Study subjects were censored if they had completed the study but did not experience any HE event during the 6 month period. For those individuals discontinuing the study for other reasons (for example, experiencing an adverse event) an assessment was still undertaken to determine if they had experienced an HE event during that period. This was done by contacting the patients who discontinued the study.

Subjects without breakthrough overt HE were censored at the time of contact or death, whichever was earlier. Therefore, complete capture was achieved for breakthrough overt HE episodes up to 6 months post randomization. Kaplan-Meier, time-to event methods were applied to these data to estimate the proportions of subjects who experienced breakthrough overt HE episodes over a 6-month time interval. Greenwood's formula for estimation of standard error (SE) was used to estimate SE at each time point. Kaplan-Meier results for each treatment group were illustrated in figures (Salix, Clinical study report RFHE3001, p.51).

The five key secondary endpoints were analysed in a hierarchical fashion. Significance tests were conducted for all secondary efficacy endpoints and the results were reported also in hierarchical order, from endpoint number 1 through number 5, until a non significant p-value was found (p>0.05)

Mean changes from baseline in venous ammonia concentrations and in CLDQ fatigue domain score were analysed by analysis of covariance.

For the remaining secondary and tertiary endpoints of RFHE3001 study, inferential statistics were undertaken. These results were not part of the hierarchical testing procedure.

Compliance was defined for a subject as the receipt of at least 80% and no more than 120% of the expected tablets. Percent overall compliance was calculated as: 100 × (total number of tablets dispensed – total number of tablets returned)/(2 × total duration of exposure).

Calculated overall compliance results were summarised descriptively by treatment group (N, mean, median, SD, minimum, and maximum values). The numbers and percentages of compliant and noncompliant subjects were also summarized by treatment group.

- ### RFHE3001: Sub-group analysis

Subgroup analysis of rifaximin treatment effect was undertaken for the primary efficacy endpoint. The following subgroups were evaluated: sex, age (< 65 versus ≥ 65 years), race (white versus non-white), analysis region (North America versus Russia), baseline MELD level (≤ 10, 11 - 18, 19 - 24), baseline Conn score (0 versus 1), prior lactulose use (yes versus no), diabetes at baseline (yes versus no), duration of current verified remission (≤ 90 days versus > 90 days), and the number of HE episodes within the 6 months prior to randomization (2 versus > 2).

- ### RFHE3001: Statistical power and determination of sample size

A Cox regression analysis of the time to first breakthrough overt HE episode was used to assess the relative risk of experiencing a HE episode. Using this information, a calculation was made to determine the necessary sample size. The resulting sample size was of 250 subjects, 125 allocated to each arm.

The null hypothesis of interest is:

H0: $\beta_{rifaximin} = 0$

Versus the alternative:

HA: $\beta_{rifaximin} \neq 0$,

where $\beta_{rifaximin}$ *is the coefficient of the treatment arm (rifaximin) in a Cox proportional hazards regression model compared to the placebo group. Thus,* $\beta_{rifaximin}$ *represents the log of the hazard ratio for comparing rifaximin to placebo and is equivalent to testing that the hazard ratio for the occurrence of an HE breakthrough overt event is significantly different from 1.*

The following assumptions were used in the calculation of sample size. Approximately 50% of rifaximin-treated subjects and 70% of placebo-treated subjects would experience a breakthrough overt HE event over the course of the 6-month treatment period, which would result in a hazard ratio for rifaximin relative to placebo of approximately 0.58 (coefficient of the treatment arm ($\beta_{rifaximin}$ = -0.54) for time to first breakthrough overt HE episode. On the basis of these assumptions, sample size calculations show that approximately 100 evaluable subjects per treatment group would provide > 80% power to demonstrate that rifaximin was superior to placebo. Approximately 125 subjects per treatment group were randomized in order to compensate for the anticipated loss of subjects due to liver transplant, GI bleeds, and other competing events (Salix, Clinical study report RFHE3001, pp.53 - 54).

- ### RFHE3002: Planned statistical analysis

As the primary goal of RFHE3002 study was to assess the long-term safety of rifaximin use, the sample size was established based on the number of subjects expected to be available, resulting in an anticipated enrolment for this open-label study of approximately 500 subjects.

The population included in RFHE3002 analysis consisted of all study subjects who received at least 1 dose of the study medication and provided at least 1 post-baseline safety assessment.

Furthermore, the study included the following populations used for analysing maintenance of effect:

- New rifaximin: Subjects who received placebo in RFHE3001 and rolled over into RFHE3002 and new subjects who did not participate in RFHE3001.
- Continuing rifaximin: Subjects who received rifaximin in RFHE3001 and rolled over into RFHE3002.

Overall study drug percent compliance was calculated based on the number of tablets dispensed and returned for each subject. The formula for the overall compliance to study drug was defined as: (sum of the number of tablets dispensed – sum of the number of tablets returned) / (duration of study drug exposure * number of tablets that should have been taken daily) * 100.

The overall compliance with study drug was summarized with descriptive statistics for each group and overall. The number and percent of subjects was also summarized in 3 categories for compliance: < 80% compliance; 80% through 120% compliance; > 120% compliance.

Treatment-emergent adverse events were defined as any event with a start date occurring on or after treatment Day 1 or, if pre-existing, worsening after treatment Day 1. If a subject experienced the same adverse event more than once, then that subject was only counted once for the summary of that adverse event, using the most severe intensity reported.

Assessments of Conn scores and asterixis grades were conducted to monitor HE status as part of the standard of care for this subject population. As RFHE3002 was a safety study, only summary statistics were performed for these analyses.

The statistical approach used for the analysis of RFHE3001 and RFHE3002 data was generally satisfactory.

4.1.8 Summary statement

The ERG is happy with Norgine's second searches which were clearly laid out and were appropriate to the task. As these second searches overlap all the first searches, the ERG is happy to assess these second searches as the main searches.

The only hesitation, as discussed above (see Section 4.1.1), is the way Norgine have expressed the name of the intervention in these second searches. Whilst 'Rifaximin-α' is technically correct, a search on 'rifaximin' – as used in the first searches – is more sensitive. Both variations of spelling return identical results in the key databases of MEDLINE and EMBASE but the second searches (using only 'Rifaximin-α') do not work properly in The Cochrane Library. The ERG cannot therefore rule out the possibility that Norgine may have missed items unique to The Cochrane Library.

The ERG would add that the contingency that a record has been missed because of this is slight. We cannot, however, definitively state this on the basis of Norgine's searching. It is worth adding that The Cochrane Library is primarily populated with records gathered from MEDLINE and EMBASE and Norgine's second searches have worked in these databases. Searches of The Cochrane Library would, however, add inclusion of items such as erratum reports, withdrawn reviews and items located by Cochrane Groups through hand-searching. It is these items which Norgine may have missed.

The submitted evidence generally reflects the decision problem defined in the submission. However, it should be noted that:

- **Population**. The analysis refers to adults with chronic liver disease who have had prior episodes of overt HE and are currently in remission. Therefore, the indication and submission do not cover patients with HE caused by an acute liver insult and patients with more severe liver disease.
- **Intervention**. Although in the scope the intervention was specified as rifaximin, in the study used for the submission 91.3% of the patients were using concomitant lactulose.
- **Comparators**. The comparator used in the analysis is placebo plus concomitant lactulose. Neomycin and neomycin with lactulose were not used as comparators.

The validity of the clinical effectiveness data and statistical approaches was considered good.

Superseded - see erratum

4.2 Summary of submitted evidence

4.2.1 Summary of results

In this section we present a summary of the clinical results. For further details, the reader is advised to go to Section 6.5, Section 6.8 and Section 6.9 of the submission report.

- RFHE3001

4.2.2 Results from RFHE3001 study are presented in Section 6.5 of the submission report. Table 4 and

Table 5 summarise the main outcomes from the study.

Table 4. Summary of RFHE3001 trial outcomes

Outcome	Value	CI 95% – lower value	CI 95%– upper value	Statistically significant	Comments
Primary endpoint results					
Time to first breakthrough HE episode (hazard ratio – rifaximin vs. placebo)	0.42	0.28	0.64	Yes	The outcome was reported in 31 of 140 (22.1%) patients in the rifaximin group and in 73 of 159 (45.9%) patients in the placebo group.
Secondary endpoint results					
Time to first HE-related hospitalisation (hazard ratio – rifaximin vs. placebo)	0.50	0.29	0.87	Yes	The outcome was reported in 19 of 140 (13.6%) patients in the rifaximin group and in 36 of 159 (22.6%) patients in the placebo group.
Time to any increase from baseline in Conn score (hazard ratio – rifaximin vs. placebo)	0.463	0.312	0.685	Yes	The outcome was reported in 37 of 140 (26.4%) patients in the rifaximin group and in 77 of 159 (48.4%) patients in the placebo group.
Time to any increase from baseline in asterixis grade (hazard ratio – rifaximin vs. placebo)	0.646	0.424	1.008	No	The outcome was reported in 32 of 140 (22.9%) patients in the rifaximin group and in 50 of 159 (31.4%) patients in the placebo group.

Table 5. RFHE3001 trial outcomes: other secondary endpoint results

Outcome	Value – rifaximin group (SD)	Value – placebo group (SD)	Statistically significant	Comments
Mean fatigue domain score on the CLDQ at baseline and end of treatment	Baseline: 3.28 (1.326) End of treatment: 3.57 (1.527)	Baseline: 3.34 (1.406) End of treatment: 3.51 (1.529)	Not reported	n/a
Mean change from baseline in venous ammonia concentration at each post baseline assessment and at end of treatment (mean change in venous ammonia level)	-5.7 (46.77)	-0.3 (58.13)	No	n/a

Time to increase from baseline in Conn score and asterixis grade should have greater emphasis than displayed in the Executive Summary provided in the submission. Hence we draw attention to details reported in the main text of the submission (pp. 54-55).

We draw attention to the fact that some of the reported outcomes are not statistically significant as per the above tables.

In subgroup analysis, it was reported that for subjects who were not receiving lactulose prior to the study, the effect of rifaximin when compared with placebo was not statistically significant (based on visual inspection, hazard ratio 95% CI ranges between 0 and approximately 3.3).

Similarly the effect of rifaximin when compared with placebo was not statistically significant for patients with a MELD score between 19-24 (based on visual inspection, hazard ratio 95% CI ranges between 0 and 1.5 approximately).

Adverse events

Adverse events also deserve greater emphasis than that displayed in the Executive Summary provided in the submission. Hence we would draw attention to further detail reported in the main text of the submission.

Because breakthrough overt HE was an efficacy outcome for the study, reported AEs (all AEs are treatment-emergent, unless otherwise stated) of HE were checked against the episodes of breakthrough overt HE. All reported AEs of HE corresponded to breakthrough overt HE episodes, with the exception of one case in one subject.

A total of 79.9% of subjects (239 of 299) experienced AEs during the course of the study, including 80% of subjects (112 of 140) in the rifaximin group and 79.9% of subjects (127 of 159) in the placebo group.

Adverse reactions in study RFHE3001 which occurred in ≥ 5% of patients receiving rifaximin and at a higher incidence than placebo are shown in Table 6*.*

Table 6. Adverse reactions occurring in ≥ 5% of patients receiving rifaximin and at a higher incidence than placebo in RFHE3001

MedDRA System Organ Class	***Event***	***Placebo N=159***		***Rifaximin N=140***	
		n	*%*	*n*	*%*
Blood and lymphatic system disorders	*Anaemia*	*6*	*3.8*	*11*	*7.9*
Gastrointestinal disorders	*Ascites*	*15*	*9.4*	*16*	*11.4*
	Nausea	*21*	*13.2*	*20*	*14.3*
	Abdominal pain upper	*8*	*5.0*	*9*	*6.4*
General disorders and administration site conditions	*Oedema peripheral*	*13*	*8.2*	*21*	*15.0*
	Pyrexia	*5*	*3.1*	*9*	*6.4*
Musculoskeletal and connective tissue disorders	*Muscle spasms*	*11*	*6.9*	*13*	*9.3*
	Arthralgia	*4*	*2.5*	*9*	*6.4*
Nervous system disorders	*Dizziness*	*13*	*8.2*	*18*	*12.9*
Psychiatric disorders	*Depression*	*8*	*5.0*	*10*	*7.1*
Respiratory, thoracic and mediastinal disorders	*Dyspnoea*	*7*	*4.4*	*9*	*6.4*
Skin and subcutaneous tissue disorders	*Pruritus*	*10*	*6.3*	*13*	*9.3*
	Rash	*6*	*3.8*	*7*	*5.0*

The majority of AEs were mild or moderate in severity. Severe AEs were experienced by 28.8% of subjects (86 of 299), including 26.1% in the rifaximin group and 30.8% in the placebo group. Drug-related AEs were reported for 20.7% (62 of 299) of subjects (19.3% rifaximin vs 21.4% placebo). Serious AEs were experienced by 38.1% (114 of 299) of subjects (36.4% rifaximin vs 39.6% placebo), and 25.1% (75 of 299) of subjects (21.4% rifaximin vs 28.3% placebo) had AEs resulting in study discontinuation. The percentages of subjects who had AEs, severe AEs, drug-related AEs, SAEs, AEs resulting discontinuation, and who died were similar between placebo and rifaximin groups (Table 7).

Table 7. Summary of AEs – safety population, study RFHE3001

Adverse events *Number (%) patients*	*Placebo* *(N=159)*	*Rifaximin* *(N=140)*	*Total* *(N=299)*
≥ 1 AE	*127 (79.9)*	*112 (80.0)*	*239 (79.9)*
≥ 1 drug-related AE	*34 (21.4)*	*27 (19.3)*	*61 (20.4)*
≥ 1 severe AE	*49 (30.8)*	*37 (26.1)*	*86 (28.8)*
Deaths	*11 (6.9)*	*10 (7.1)*	*21 (7.0)*
1 SAE	*63 (39.6)*	*51 (36.4)*	*114 (38.1)*
≥ 1 drug-related SAE	*3 (1.9)*	*4 (2.9)*	*7 (2.3)*
Discontinuation due to AEs	*45 (28.3)*	*30 (21.4)*	*75 (25.1)*

Abbreviations: AE, adverse event; SAE, serious adverse event

AEs were most frequently reported in the following system organ classes (SOCs; rifaximin vs placebo): GI disorders (51.4% vs 42.1%), nervous system disorders (37.9% vs 40.3%), general disorders and administration site conditions (40% vs 32.7%), infections and infestations (32.9% vs 30.8%), and respiratory, thoracic and mediastinal disorders (25.7% vs 24.5%). The most common AEs (rifaximin vs placebo) were: diarrhoea (10.7% vs 13.2%), nausea (14.3% vs 13.2%), peripheral oedema (15% vs 8.2%), fatigue (12.1% vs 11.3%), dizziness (12.9% vs 8.2%), ascites (11.4% vs 9.4%), and headache (10% vs 10.7%). Episodes of HE that qualified as SAEs were recorded for 12.1% of rifaximin subjects vs 21.4% of placebo subjects.

The rifaximin group had higher incidences of anaemia (7.9% with rifaximin vs 3.8% with placebo), peripheral oedema (15% vs 8.2%), pyrexia (6.4% vs 3.1%), arthralgia (6.4% vs 2.5%), and dizziness (12.9% vs 8.2%) than the placebo group. Subjects in the rifaximin group also had a higher incidence of AEs in the eye disorders SOC than subjects in the placebo group: 9.3% (13 of 140) vs 1.9% (3 of 159), respectively. No subject had an eye disorder AE that resulted in study discontinuation.

… The proportions of subjects who had severe, drug-related AEs were higher in the rifaximin (8 of 140) than in the placebo (4 of 159) group. The severe, drug-related AEs were abdominal pain, balance disorder and confusional state, dizziness, diarrhoea, clostridium colitis and HE, clostridium colitis, ascites and HE, and HE in 1 subject each in the rifaximin group, and HE (2 subjects), abdominal pain (1 subject), and nausea (1 subject) in the placebo group.

... The frequency of subjects who had special interest AEs were similar between treatment groups (24.3% for rifaximin vs 22% for placebo). Diarrhoea was the most common special interest AE (10.7% and 13.2%, rifaximin vs placebo), followed by bacterial peritonitis (1.4% vs 2.5%).

Higher proportions of rifaximin treated subjects vs placebo-treated subjects experienced pneumonia (2.9% vs 0.6%), haematochezia (1.4% vs 0.6%), and gastritis and clostridium colitis (each in 1.4% vs 0 subjects).

(Submission pp.71-77)

- RFHE3002

The main objective of RFHE3002 follow-up study was to evaluate the long-term safety and tolerability of rifaximin in patients with a history of HE. Results were reported in Section 6.8 of the Submission report.

Time to first breakthrough HE episode was obtained for patients continuing rifaximin from study RFHE3001 compared with RFHE3001 placebo group. The resulting hazard ratio was not presented, although a Kaplan Meier function was reported (Figure 14 of the Submission report, p.68)

Changes from baseline in Conn score and in asterixis score, as well as number of hospitalisations were also presented for patients continuing rifaximin vs. patients new to rifaximin (Submission, pp.68-69).

Adverse events

Adverse events also deserve greater emphasis than that displayed in the Executive Summary provided in the submission. Hence we would draw attention to further detail reported in the main text of the submission (p81).

Adverse events that were considered to be related to study drug were recorded for [redacted] of subjects. AEs considered related to study drug in ≥ 1% of subjects (i.e. three or more subjects) were

[redacted]

4.2.3 Critique of submitted evidence synthesis

No meta-analysis was required as only one RCT and one single-arm non-RCT were relevant to the decision problem.

4.2.4 Summary of clinical effectiveness

It is likely that the clinical systematic review of the literature undertaken by Norgine contains all the relevant studies. The submitted evidence reflects the decision problem adequately even though it parted from NICE original scope, especially in terms of population and comparators covered.

The submission from Norgine included two studies: a good quality RCT, RFHE3001, n=299 (Bass et al, 2010; CSR RFHE3001) and a non-RCT, RFHE3002, n=322 (CSR RFHE3002).

RFHE3001 was a Phase III randomised, double-blind, placebo-controlled study conducted over a 6 month period. The main objective of the study was to evaluate the efficacy of rifaximin (550

mg twice a day) compared with placebo, in patients who were in remission from recurrent, overt, episodic HE resulting from chronic liver disease. 140 patients were randomised to the rifaximin arm and 159 patients were randomly allocated to the placebo arm. Patients in the rifaximin arm were treated with rifaximin and lactulose combined, while patients in the placebo arm were treated with lactulose alone.

RFHE3002 was an open-label Phase III study. The main objective of the study was to provide long-term evaluation of the safety and tolerability of rifaximin. Patient who successfully completed the Phase III RCT (RFHE3001) were eligible to participate in study RFHE3002 in addition to new patients.

The manufacturer's submission summarised the identified benefits as:

- Rifaximin 550 mg twice a day plus lactulose significantly reduced ($p<0.001$) the relative risk of recurrence of overt HE episodes by 58% (hazard ratio 0.42, 95% confidence interval (CI), 0.28 to 0.64) vs. placebo plus lactulose over 6 months.
- Rifaximin 550 mg twice a day plus lactulose significantly reduced ($p=0.01$) the relative risk of hospitalisation involving HE by 50% (hazard ratio 0.50, 95% CI, 0.29 to 0.87) vs. placebo plus lactulose over 6 months.
- Norgine indicated that the incidence and seriousness of adverse events reported during the study was similar between the rifaximin and placebo groups. However they did not present relative risks and risk difference and associated 95% confidence intervals for each adverse event, which would have provided a stronger case for their decision of not costing adverse events.
- RFHE3002 showed that long term treatment over 24 months with rifaximin 550 mg twice a day plus lactulose provided continued protection from HE and reduced the hospitalisation rate.

Mortality data from trial RFHE3001 was considered not to be mature enough to capture the drug overall impact on survival. However the model captures the effect of rifaximin vs. placebo on mortality by reducing the recurrence of HE events, and the reduced mortality rate associated with that reduction is a major source of QALYs gained.

Overall, the clinical data reported in the submission was consistent with Bass et al (2010) and the CSRs from RFHE3001 and RFHE3002.

5.0 Economic evaluation

In this chapter, we assess the cost-effectiveness analysis submitted by Norgine. Overall, we found Norgine's economic model and evaluation to be good.

We start with a summary of the systemic review of cost-effectiveness studies presented by Norgine and the methods used in the economic evaluation (Section 5.1). Then we present a critique of the methods they used (Section 5.2). This is followed by a description of Norgine's results (Section 5.3) and our comment on their validity (Section 5.4).

5.1 Overview of manufacturer's economic evaluation

5.1.1 Summary of Norgine's systematic review of cost-effectiveness studies

- #### Description of manufacturer's search strategy and comment on whether the search strategy was appropriate

Two searches were performed for cost-effectiveness.

Search - submission

Bibliographic searches were initially conducted on May 12th 2011 in the following databases:

- Embase Biomedical Answers (Elsevier): data parameters not provided
- The Cochrane Library Issue 5 CDSR and Issue 2 Central and other databases (2011)
- NHS Economic Evaluation Database
- Econlit (OVID)

A search of the following web-sites and web-resources was made in May 2011:

- Canadian Agency for Drugs and Technologies in health
- Pharmacology and Therapeutics Advisory Committee
- Scottish Medicine Consortium
- NICE
- Centre for Reviews and Dissemination Databases (DARE, NHS EEDS and HTA)

The cost-effectiveness search used a different search strategy from the effectiveness search. The (first) cost-effectiveness search took terms for the population (hepatic encephalopathy) and the primary intervention (rifaximin). The manufactures submission states that the search was not limited by date and that no database restrictions were applied. This is not, however, clear and replicable from their search write up (p189).

There are two issues to raise on this search. The first issue is that the population thesaurus term was limited to drug effects and this is not therefore a full and sensitive expression of the

primary population indexing term. The second point is Norgine's use of Elsevier's Biomedical Answers platform.

This platform does not combine all EMBASE and MEDLINE content in one platform (as Norgine state p188) as it does not presently include MEDLINE In-Process records. This means that new content (which is in the process of indexing into MEDLINE), or content which is without indexing, would have been missed by Norgine on this first search. It is worth noting that this is also in breach of the specification for manufacturer's evidence (NICE: June 2012). We raise this as, in the first instance, this first search will have informed the creation of the model and the literature used for this purpose may not have been up-to-date.

Search - clarification

In clarification, Norgine confirmed additional (second) searches had been run on December 13th 2012. This second search is more sensitive than the first cost-effectiveness search with the only comment being that the primary intervention is expressed as rifaximin-α and not also as Rifaximin, which would have improved sensitivity (as at 4.1.1). As explored in the effectiveness section, this decision may have led to omissions in the Cochrane searches.

This additional search included searches of the following conference proceedings:

- European Association for the Study of the Liver (EASL)
- United European Gastroenterology (UEG);
- American Gastroenterological Association (AGA)
- American Association for the Study of Liver Disease (AASLD)

The second search used the following bibliographic databases:

- MEDLINE (R) In-Process & Other Non-Indexed Citations and OVID MEDLINE(R) 1946 through the date of the search (13 Dec 2012).
- EMBASE via OVID 1988 to 2012 week 49.
- The Cochrane Library via OVID (CENTRAL, DARE, CDSR, HTA and NHS EEDS)
- Econlit via OVID 1961 through the date of the search (13 Dec 2012).

• Search results

The first search identified one economic study (Huang et al, 2007). This study was subsequently excluded from the submission as the population studied does not reflect the current decision problem as per the licensed indication for rifaximin in the UK (i.e. reduction in recurrence of episodes of overt HE).

The second search identified two potentially relevant economic evaluations (Bajaj et al and Paul et al) since 2010.

On full review Bajaj et al (2012) was not considered to be relevant as the study assesses the cost effectiveness of diagnosis as well as treatment and the outcome was reduction in motor vehicle accidents and therefore does not address the current decision problem.

Paul et al (2012) was considered to be relevant but not enough data was available in order to assess this study in adequate detail as it was presented as a conference abstract only. Furthermore, as this study states it is an update of the analysis completed by Huang et al (2007), it could be assumed that criticisms of Huang et al would still apply. For example, the patient population does not match that of the current decision problem (no prior episode reported) and there is not enough detail provided on how clinical benefits were included in order to reproduce the results of the study.

Therefore, none of the economic evaluations identified addressed the main outcome in the decision problem (i.e. reduction in the recurrence of HE). For this reason a de-novo analysis was undertaken.

5.1.2 Norgine's economic model submitted to NICE

We now turn to the economic evaluation that Norgine presented to NICE. Norgine reports cost per QALY estimates for rifaximin plus optional concomitant lactulose versus placebo plus optional concomitant lactulose in patients in remission from recurrent episodes of overt HE.

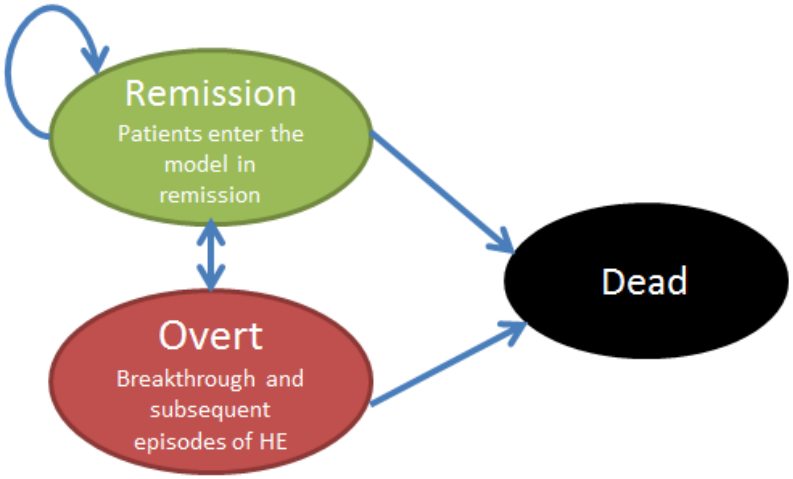
The model was built in Microsoft Excel© 2010. Here, we summarise the main features of the model. In general, we consider it to be well structured and coded appropriately. Some errors were found, however the impact of these on the final ICERs is not considered to be significant. These issues are discussed in the following sections of this report.

Norgine cost-effectiveness analysis relied greatly on the extrapolation of the RFHE3001 and RFHE3002 trial data. Particularly the choice of the lognormal distribution to fit these data and the combination of the data from both trials are two key components in the economic model and main drivers of the final ICER. Section 5.2.3 of the report includes an extensive examination of their application in Norgine's analysis. The appropriateness of the methods employed by Norgine and their impact on the outputs of the economic analysis are also examined.

- #### Natural history

Norgine's cost-utility model was developed using a state transition Markov approach. The structure of the model, illustrated in Figure 1, is argued to be appropriate and reflective of the clinical pathway of HE.

Figure 1. Norgine's model structure



The model describes three health states:

- Remission: all patients enter the model in the remission state.
- Overt: this health state captures the primary outcome of the cost-effectiveness analysis which is time to first breakthrough HE episode. It also captures time to subsequent HE episodes.
- Death: this is the absorbing state of the model.

All patients enter the model in the remission state. Patient population consists on adults (≥ 18 years old) in remission from previous episodes of HE.

Patients can then experience their first breakthrough HE episode, moving to the overt state, from which they are always assumed to go back to the remission state. Once patients are back in the remission state, they can experience subsequent HE episodes moving again to the overt state. Patients can die while in remission or in the overt state.

In the manufacturer's report it is stated that the model cycle length is a month, however there is also mention to cycles of 28 days. A half-cycle correction was not applied in the Markov structure as it was argued to be unnecessary given the relatively short cycle length.

Even though the cost-effectiveness model focused on HE and its progression, all patients suffering from HE in the economic analysis are liver disease patients. In this sense, all patients in the model suffer from the progression of their liver disease over time. Patients suffering from liver disease also experience a wide range of symptoms that vary with disease severity. Mortality was adjusted to reflect disease progression.

• Treatment effectiveness within submission

Treatment effectiveness within the model works essentially through transition probabilities between the remission and the overt states. Even though there was the potential for rifaximin to improve overall survival by reducing the recurrence of HE episodes, mortality data from trial RFHE3001 was considered not to be mature enough to capture the drug overall impact on survival.

Transition probabilities from remission to overt state in the model were derived from survival functions based on time-to-event data from RFHE3001 clinical trial and the RFHE3002 follow-up study. While the transition probabilities from remission to first breakthrough HE episode were estimated as time-dependant, meaning that in each cycle the probability of experiencing an event changes, the transition probabilities from remission to subsequent HE episodes were estimated as constant over the 5 year period.

Data from RFHE3001 and RFHE3002 were used in the following ways to compute transition probabilities within the model:

- Remission to overt (first breakthrough episode): for the rifaximin arm, time to first breakthrough data was extracted and combined from both Kaplan-Meier (KM) plots in RFHE3001 and RFHE3002. A lognormal distribution was used to fit the combined dataset (RFHE3001 and RFHE3002) for rifaximin patients in order to extrapolate the study results to a 5 year horizon (Table 8). For the placebo arm, a lognormal distribution was fitted to the RFHE3001 study data alone and the shape parameter from this regression was replaced with the shape parameter estimated with the combined dataset (Table 9).
- Remission to overt (subsequent episodes): data from RFHE3001 was also used to model the risk of experiencing subsequent HE episodes. An exponential curve was fitted to the KM plot of time to first breakthrough, then obtaining the hazard ratio for rifaximin versus placebo (Table 10). Time-independent discrete transition probabilities were estimated from the instantaneous hazard rates.

The coefficients from the three regressions are presented in Table 8, Table 9 and Table 10.

Table 8. Regression results for lognormal distribution fitted to the combined dataset (RFHE3001 and RFHE3002) for rifaximin arm

_t	Coef.	Std. Err.	z	P>z	95% Confidence Interval	
_cons	4.011754	0.318262	12.61	0	3.387972	4.635535
/ln_sig	1.015887	0.104512	9.72	0	0.811048	1.220725
sigma	2.761811	0.288641	-	-	2.250265	3.389646

Table 9. Regression results for lognormal distribution fitted to RFHE3001 alone for placebo arm

_t	Coef.	Std. Err.	z	P>z	95% Confidence Interval	
_cons	1.994058	0.19677	10.13	0	1.608396	2.379719
/ln_sig	1.015887	0.104512	9.72	0	0.811048	1.220725
sigma	2.761811	0.288641	-	-	2.250265	3.389646

Table 10. Regression results for exponential distribution fitted to RFHE3001 data for rifaximin and placebo arms

_t	Coef.	Std. Err.	z	P>z	95% Confidence Interval	
RIF	-0.89478	0.215273	-4.16	0	-1.31671	-0.47285
_cons	-2.15949	0.118678	-18.2	0	-2.39209	-1.92688

Effectiveness data from RFHE3001 were also used to derive secondary outcomes. These were not converted into transition probabilities but were used to compute certain model parameters:

- Overt HE-related hospitalisation: the key secondary efficacy endpoint in study RFHE3001 was time to first HE-related hospitalisation. The percentage of patients hospitalised, given they had experienced an overt HE episode, for both the rifaximin and placebo arms is reported in Table 11. These data were then used to cost the overt health state in the economic model.
- Conn score for HE episodes: the scores reported in RFHE3001 study (presented in Table 12) were used to inform the calculation of health related quality of life for the overt and the remission states, as well as the mortality rates used in the economic model.

Table 11. Patients hospitalised at 6 months

Treatment	Percentage of patients hospitalised at 6 months
Rifaximin	61.29%
Placebo	49.32%

Table 12. Breakdown of total HE episodes by Conn score

	Conn score 1	Conn score 2	Conn score 3	Conn score 4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- ## Health related quality of life

Study RFHE3001 reported health related quality of life (HRQL) data using the SF-36 questionnaire. In their report Norgine highlighted that there were difficulties in getting patients to self-rate their health while experiencing an overt episode. It is also mentioned that the completion of the SF-36 questionnaire occurred at discrete points in time (every 28 days). Hence Norgine concluded that given the short duration and infrequent occurrence of episodes of HE, it was unlikely that the use of a generic instrument such as the SF-36 at discrete intervals would have captured the detrimental quality of life effects associated with HE episodes.

In light of the previous argument, Norgine ran a number of literature searches of HRQL data but the conclusion was that none of the identified studies were suitable for the analysis.

Search - submission

Bibliographic searching was initially conducted in May 2011 in the following databases:

- Embase Biomedical Answers (Elsevier)
- The Cochrane Library
- NHS Economic Evaluation Database
- PubMed (NLM)

This search was updated in February 2012 in PubMed (alone) using a different search strategy.

For the first search, terms for the population (hepatic encephalopathy) and the primary intervention (rifaximin) were used.

As with the first cost-effectiveness search, the thesaurus term for hepatic encephalopathy was limited to drug effects. This search also used the EMBASE Biomedical Answers platform which, as mentioned in previous sections, does not include MEDLINE In-Process and so this search has not searched all the relevant databases for submission.

This first search was updated with a PubMed search. This search used terms for hepatic encephalopathy combined with the following terms; utility weight, utility value, preference weight or quality of life weight.

On their own, these searches were inadequate to the task however, in clarification, Norgine provided second searches which had been run on December 17th 2012.

Search - clarification

The following databases were searched:

- Medline (OvidSP) 1946 through the date of the search (17 Dec 2012).
- Medline In-Process & other non-indexed citations (OvidSP)
- Embase (OvidSP) 1988 to 2012 week 49

- Econlit (OvidSP) 1961 through the date of the search (17 Dec 2012).
- NHS EED

In addition, research abstracts were searched for the 2011 and/or 2012 annual meetings of the following organizations:

- European Association for the Study of the Liver (EASL)
- United European Gastroenterology (UEG)
- American Gastroenterological Association (AGA)
- American Association for the Study of Liver Diseases (AASLD)

This search is more sensitive than the first search with the only comment being that the primary intervention is expressed as rifaximin-α and not also as rifaximin, which would have improved sensitivity (as at 4.1.1). As discussed in the effectiveness and cost-effectiveness sections, this decision may have led to records being missed in the Cochrane searches.

The following criteria for selecting studies were used:

- Not reporting on HE.
- Quality of life studies that did not report preference based utility weights (publications which were based on transformations of HRQL instruments to utilities were excluded), or did not report utility values.
- Were not a quality of life study.

None of the identified studies were considered suitable for the analysis. Norgine concluded that there was a justification for eliciting utility values for relevant health states from the public using the time trade off (TTO) approach and standard gamble (SG). TTO values were used in the base case analysis while SG utility values were used in sensitivity analysis. Utility values used for the three states of the economic model are presented in Table 13.

Table 13. Health states utility values

Health state	Utility value	Confidence interval	Source
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

• Resources and costs

The model submitted by Norgine used costs based on the NHS perspective. Costs included in the model are drug costs and disease management costs (such as outpatient visits and hospital stays).

Estimates of resource use were obtained from expert opinion and no systematic review was undertaken to identify resource data. As HE is a condition predominately managed in the secondary healthcare setting, Healthcare Resource Group (HRG) procedure codes and NHS Reference Costs were used to estimate disease management costs. Table 14 reports the costs associated with each health state in the model.

Adverse events were not costed. Norgine considered that the proportions of patients experiencing adverse events were comparable between the rifaximin and placebo groups. In the safety study (RFHE3002) possibly treatment-related events were reported for [redacted] of patients.

Table 14. Health state costs

Health state	Item	Value		Total	
		Rifaximin	Placebo	Rifaximin	Placebo
Remission	Drug	£288.34	£7.31	£325.23	£44.2
	Outpatient attendance	£36.89	£36.89		
Overt	Drug	£288.34	£7.31	£648.07	£300.27
	Inpatient hospital stay	£249.05	£182.28		
	Outpatient attendance	£110.68	£110.68		

Costs - rifaximin acquisition costs

The cost of rifaximin was based on patients receiving an average daily dose of 1100mg per day. For the cost of lactulose, different mean doses for the rifaximin and the placebo arms were used. The mean dose of concomitant lactulose on the rifaximin arm was 3.14 cups per day (the equivalent to 47.1 ml per day) and 3.51 cups per day (the equivalent to 52.65 ml per day) for patients on the placebo arm.

The unit price of a 56 tablet of rifaximin amounted to £259.23 per pack as specified in the British National Formulary (BNF) and the price of lactulose was £2.28 per 500mlas per the BNF. Table 15 presents the breakdown of the drug cost for each arm of the economic model.

Table 15. Health state drug costs

	Units	Avg. daily dose	Unit size	Unit price	Cost per month	Total cost
Rifaximin	mg	1,100	550	£4.63	£281.80	£288.34
Lactulose	ml	47.10	500	£2.28	£6.54	
Lactulose	ml	52.65	500	£2.28	£7.31	£7.31

Costs - resource use and costs associated with HE

Within their economic model, Norgine based the estimates of ongoing resource use on expert opinion. These were then used to calculate the resource cost within each cycle of the model. In order to do this, NHS Reference Costs for 2011/12 were applied.

The use of resources consisted of hospital attendance (outpatient visits and hospital stay):

- For patients in remission, the frequency of outpatient visits was assumed to be every 3 months.
- For patients in the overt state, the frequency of outpatient visits was assumed to be one visit per HE episode. A proportion of patients also incur hospitalisation costs. This proportion differs for the rifaximin and the placebo arms. The mean length of stay for these patients was assumed to be 5 days and the cost per day in hospital was obtained by weighting the costs associated with selected non-elective inpatient HRG procedures by their frequency.

Table 16 reports the HRG procedures utilised in the computation of the cost per day in hospital.

Table 16. HRG procedures considered for the cost per day in hospital

Currency code	Frequency	National average unit cost	Bed days	Average length of stay - days	Cost per day	Currency description
GC01A	1,293	£3,484	13,676	10.58	£329.38	Liver Failure Disorders with Interventions
GC01B	2,427	£2,028	14,067	5.80	£349.97	Liver Failure Disorders without Interventions
GC15A	2,419	£3,988	30,302	12.53	£318.38	Non-Malignant Liver Disorders with Catastrophic CCs
GC15B	2,708	£3,084	26,066	9.63	£320.40	Non-Malignant Liver Disorders with Severe CCs
GC15C	7,821	£2,421	57,096	7.30	£331.64	Non-Malignant Liver Disorders with Major CCs
GC15D	12,09	£1,795	61,262	5.07	£354.35	Non-Malignant Liver Disorders without Major CCs

- ### Discounting

All costs and health benefits were discounted at a 3.5% rate as recommended by NICE.

- ### Sensitivity analysis

Deterministic and probabilistic sensitivity analyses (PSA) were undertaken by Norgine. The outputs are reported in Section 5.3 of this report. Norgine claims that one-way sensitivity analysis was conducted on all the model parameters, with the exception of the percentage of patients with a Conn score of 1, 2, 3 and 4 at first HE episode. Norgine also claims having undertaken PSA on all parameters in the model. Distributions used were reported.

No sensitivity analysis was performed on the discount rate. Exclusion of other parameters from the sensitivity analysis is discussed in Sections 5.3.1 and 5.3.2.

- ### Model validation

It is stated by Norgine that a model validation checklist including double checking of input parameters, sources, references and calculations was used.

For external validation, Norgine stated that an external health economist and reviewer validated the model. It is also mentioned that expert opinion was sought from UK liver specialists to validate the clinical pathway in the model.

No other validation was provided and neither cross-reference nor cross-testing were reported.

5.2 Critique of approach used

In this section, we comment on Norgine approach and methodology. First, we consider the model against checklists of good practice. Then we critically appraise the model structure and data as well as the methods used in the cost effectiveness analysis.

5.2.1 Critical appraisal frameworks

Norgine's economic analysis was assessed against three widely used study quality checklists for economic models:

- NICE Reference Case (NICE, 2008).
- Drummond assessment criteria (Drummond et al., 1997).
- Criteria for decision model-based economic evaluations (Philips et al., 2006).

Table 17. Critical appraisal checklist based on NICE Reference Case (NICE, 2008)

NICE reference case requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by NICE	✓	The trial population slightly differs from typical UK treatment population (see comments in Table 18)
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	?	Neomycin was excluded from the analysis as a comparator
Perspective on costs	NHS and PSS	✓	NHS
Perspective on outcomes	All health effects on individuals	✓	
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based on a systematic review	?	Based primarily on single trial (RFHE3001) evidence
Measure of health benefits	QALYs	✓	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	✓	The method used to valuate health states was generally sound, even though model performance was not undertaken.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	✓	Based on general population using TTO. Patient characteristics matched those of the trial patients.
Discount rate	3.5% pa for costs and health effects	✓	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓	

Note: ✓ indicates 'clear'; X indicates 'concerns'; ? indicates 'some concerns'.

Table 18. Critical appraisal checklist from Drummond and colleagues (Drummond et al. 1997)

Item	Critical appraisal	Reviewer comment
Is there a well defined question?	✓	In agreement with the scope
Is there a clear description of alternatives (i.e. who did what to whom, where, and how often?)	✓	In agreement with the scope
Has the correct patient group/population of interest been clearly stated?	?	The trial population slightly differs from typical UK treatment population. NICE final scope specified a population of adults who had experienced prior episodes of HE in the past. Norgine analysis departs from this in the following aspects: • Norgine addressed HE episodes in adults with chronic liver disease. • Norgine also narrowed the analysis to patients who had suffered previous overt HE episodes. • Norgine considered episodic HE. • Norgine analysis excluded patients with a MELD score ≥25, thus excluding from the analysis patients with more severe liver disease.
Is the correct comparator used?	?	Neomycin was excluded from the analysis as a comparator (contrarily to the indication on the scope). There are not sufficient available data to fully explore the appropriateness of this. We present a scenario analysis on this subject in Section 6.
Is the study type reasonable?	✓	A Markov structure for the cost-utility analysis was used
Is the perspective of the analysis clearly stated?	✓	UK NHS
Is the perspective employed appropriate?	✓	NHS Reference Costs
Is the effectiveness of the intervention established?	✓	Quality of RFHE3001 is good. Rifaximin plus lactulose prevents and delays recurrence of HE episodes compared with lactulose and placebo. More details can be found in Section 4.
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	✓	A 60 months time horizon was used. After 60 months, virtually 90% of patients modelled are dead. Alive patients are expected to be patients with stable liver disease.
Are the costs and consequences consistent with the perspective employed?	✓	All costs are presented from the UK NHS perspective

Item	Critical appraisal	Reviewer comment
Is differential timing considered?	✓	All future costs and benefits are discounted with a 3.5% rate.
Is incremental analysis performed?	✓	n/a
Is sensitivity analysis undertaken and presented clearly?	✓	Deterministic and probabilistic sensitivity analyses are reported.

Note: ✓ indicates 'clear'; X indicates 'concerns'; ? indicates 'some concerns'.

Table 19. Critical appraisal checklist of Philips et al (2004) for model-based analysis

Dimension of quality		Critical appraisal	Comments
Structure			
S1	Statement of decision problem/objective	✓	Rifaximin plus lactulose versus lactulose for the reduction in recurrence of episodes of HE.
S2	Statement of scope/perspective	✓	NHS perspective was implemented. Cost and benefit inputs were consistent with this. Scope of the model stated.
S3	Rationale for structure	✓	A cost-utility model using a state transition Markov approach is appropriate.
S4	Structural assumptions	?	Generally, model assumptions were clearly explained in the model. We are mainly satisfied with the structural assumptions even though the assumption of modelling subsequent episodes with a constant probability posed some questions and was considered not to be reflective of reality. This is explored in other sections of this report.
S5	Strategies / comparators	?	The exclusion of neomycin as stipulated in the NICE scope raised some questions. This is explored in other sections of this report.
S6	Model type	✓	A cohort model is appropriate in this case.
S7	Time horizon	✓	A 60 months time horizon was used. After 60 months, virtually 90% of patients modelled are dead. Alive patients are expected to be patients with stable liver disease.
S8	Disease states / pathways	✓	The health states used are: Remission, Overt (first and subsequent HE episodes) and death. These are appropriate to capture disease progression over time.

Dimension of quality		Critical appraisal	Comments
S9	Cycle length	✓	One month cycles are appropriate. However there was some inconsistency in calculations throughout the model as 30 days and 28 days were both considered as a one month cycle. This was corrected by the ERG to always use a 30 day cycle.
Data			
D1	Data identification	✓	Data identification methods were generally well described.
D2	Pre-model data analysis	?	More details on the extrapolation method and transition probabilities calculation could have been provided.
D2a	Baseline data	✓	Baseline data from RFHE3001 double-blind trial, which is appropriate.
D2b	Treatment effects	?	Base case treatment effect was estimated with survival analysis. A lognormal distribution was used to fit the data separately for treatment arms. A combined dataset (RFHE3001 and RFHE3002) was used for the rifaximin arm. More details on the extrapolation method and transition probabilities calculation could have been provided.
D2c	Quality of life weights (utilities)	✓	The method used to valuate health states was generally sound, even though model performance was not undertaken.
D3	Data incorporation	✓	Data inputted in the model is generally well referenced with some small exceptions. Its implementation was overall clear. For the PSA, the choice of distribution for each parameter has been described but not always justified.
D4	Assessment of uncertainty	?	A PSA is presented but the implications are not fully explored.
D4a	Methodological	✓	Different discount rate could have been used to assess the impact on model outcomes.
D4b	Structural	✓	Sensitivity analysis could have been used to assess the impact of varying probability of subsequent HE episodes.
D4c	Heterogeneity	✓	No subgroup analysis was undertaken. This is considered appropriate as patients' characteristics were homogeneous. Additional subgroup analysis was undertaken as to assess treatment differences. Two subgroups were included, subgroup A where all patients received lactulose together with rifaximin and subgroup B, where patients received rifaximin alone. More details can be found in Section 5.3.1.

Dimension of quality		Critical appraisal	Comments
D4d	Parameter	✓	Probabilistic and deterministic analyses were undertaken.
Consistency			
C1	Internal consistency	✓	Input parameters, sources, references and calculations were considered to be generally sound.
C2	External consistency	?	Only expert opinion was sought for external validation.

Note: ✓ indicates 'clear'; X indicates 'concerns'; ? indicates 'some concerns'.

5.2.2 Critique of the modelling approach and structure

The structure of the cost-utility model submitted by Norgine is relatively simple and straightforward.

The use of the remission state as starting point in the model is appropriate for the indication of rifaximin for reducing the recurrence of episodes of overt HE. Similarly the overt state is consistent with the clinical outcomes experienced by patients suffering from HE overt episodes. The overt state combines first event of an HE episode with subsequent events. However the transition probabilities from and back to remission were not the same for first HE episode and subsequent ones. We found it easier to breakdown these health states and have a clearer structure, nevertheless a technically equivalent one. This is explored in the next subsection.

A 60 months time horizon was used in the model. Even though around 10% of patients remained alive at the end of the 5 year period, the time frame seems sensible and suited to capture the benefits and costs related with HE. We have consulted our expert clinical advisor to validate the time horizon employed in the model and the 10% surviving patients are considered to likely account for patients with stable liver disease.

It is not clear in the manufacturer's report what the model cycle length is. The same issue was present in Norgine's economic model where the cycle length was sometimes considered to be 28 days and others 30.4 days. For the sake of consistency we have updated all values in the economic model so that the cycle length in every parameter calculation reflected a month duration of 30.4 days. The impact on the model outputs resulting from changing the cycle length are explored in Section 6 of the report. A half-cycle correction was not applied. We agree with Norgine that half-cycle correction was not required in the model.

From a conceptual perspective, the inclusion of lactulose in both arms of the economic model raised some initial questions. After consulting with our clinical expert and upon Norgine's reply to why this was the approach taken, it is our opinion that the inclusion of lactulose reflects current practice.

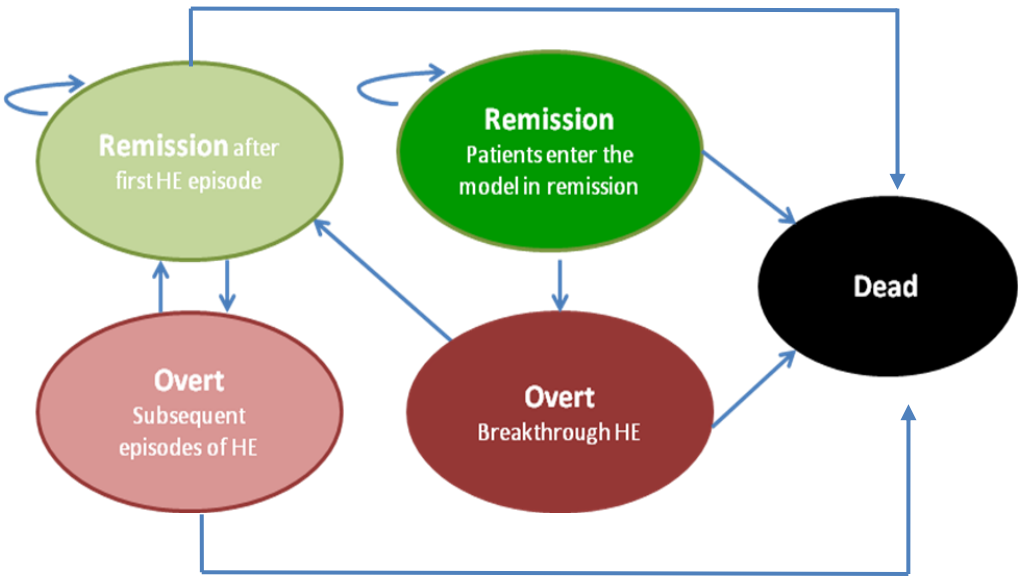
Therefore it is important to indicate that the effectiveness reported in the economic analysis undertaken by Norgine is a result of 91.3% of patients using rifaximin with concomitant lactulose and only 8.7% taking rifaximin alone. It is crucial to reinforce that all results presented in Norgine's analysis are conditional on these characteristics.

- An alternative representation of the Norgine model

In this section we report an alternative representation of Norgine's economic model. We found that this structure helps making clear the different transition probabilities between health states used in the model.

The cost-utility model developed by Norgine reported all transition probabilities consistently with Figure 2 hence no calculations were undertaken to reflect this alternative model structure.

Figure 2. Alternative representation of Norgine's model



5.2.3 Data inputs

- Patient group

The modelled patient group is reflective of the population on the RFHE3001 study on which the analysis is based. As noted in Section 5.2 there are differences between the trial population and the typical presenting UK population. However after consulting with our expert clinical advisor we believe that these differences are comparable to the differences between the general population and liver disease patients.

In addition only patients with chronic liver disease were included in the analysis. This means that patients suffering from HE resulting from acute liver failure were excluded from the analysis.

Finally patients with more severe liver disease (MELD score ≥25) were also excluded from the analysis. Norgine mentioned that even though patients with more severe liver disease have not been included in the analysis, the results are still applicable to this population. We question the validity of this assumption for the following reasons:

- In Norgine subgroup statistical analysis, MELD score category between 19 and 24 (the most severe category in RFHE3001 patient group) showed to be a predictor factor for non significance of treatment effect between rifaximin and placebo groups.
- The study provided as evidence for the effectiveness of rifaximin in patients with MELD scores ≥20 (Hassest, et al 2001) is a poor quality study (only descriptive).

• Clinical effectiveness data

The main source for clinical effectiveness data was RFHE3001 study, complemented with data from RFHE3002. These data were then used directly or indirectly to inform the calculation of transition probabilities within the model. This process is further explored in the next subsection.

Data from trial RFHE3001 were also used to estimate the percentage of patients falling into the different Conn score categories, within the total of patients experiencing an HE episode. These estimates were then utilised in the computation of other model parameters, for example utility values and mortality rates. However the total percentage of patients did not add up to 100%. This is due to lack of information on the Conn score for HE episodes in all patients (for example, 7 patients in the placebo arm of the model did not have available information on the Conn score associated with their HE episode). An adjustment should have been made so that only the population with available information was considered for the needed calculations. The impact of this adjustment is explored in the sections below in Section 6.

In general there was no problem with the use of hospitalisation data.

A small inconsistency was also found with regards to the number of patients experiencing an HE episode. In the report submitted by Norgine it is stated that the number of HE episodes verified in the rifaximin arm adds up to 31 while in the placebo arm this value amounted to 73 for the ITT population. Furthermore these values were also used in calculations relating with the proportion of hospitalised patients who have previously experienced an HE episode. However, when considering the number of HE episodes within each model arm for the categorisation by Conn scores, the total number of patients presented as having an HE episode adds up to 30 patients in the rifaximin arm and 70 patients in the placebo arm.

• Data extrapolation process

Throughout the model, treatment effectiveness is mainly represented by the transition probabilities between the different health states (Figure 1). To estimate these, Norgine used

data from RFHE3001 and RFHE3002 through different methods. These are explored in detail in this section.

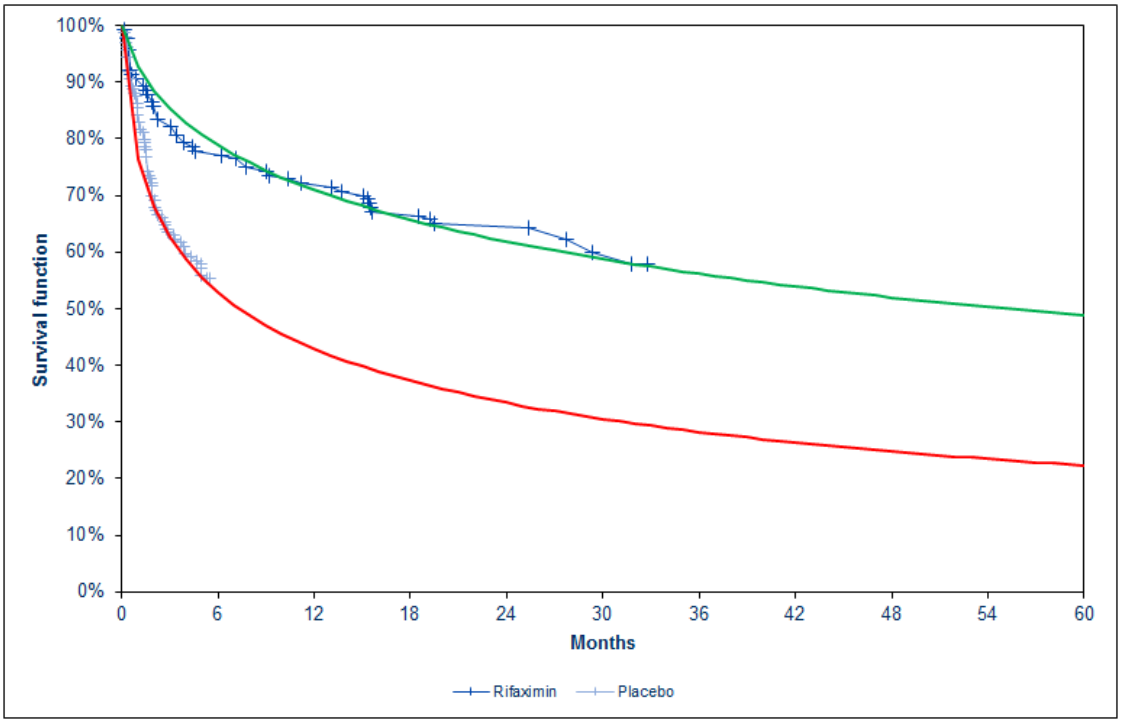
To obtain transition probabilities across health states over 5 years, Norgine extrapolated the trial data from study RFHE3001 since its duration was only 6 months. Norgine also used combined data from trial RFHE3001 and RFHE3002 follow-up study, which ran for 2 years. The combined dataset was also extrapolated to 5 years.

Remission to overt state (first breakthrough)

Rifaximin arm: To calculate the probability of experiencing a first HE episode over 5 years in the rifaximin arm, Norgine used the combined dataset extrapolated over the 5 year time horizon. The combined dataset included patients from RFHE3001 who were treated with rifaximin and maintained remission for the duration of the 6-month trial and were then followed during the follow-up study RFHE3002. After combining the available data for this group of patients, a lognormal distribution was used in order to extrapolate the study results over 5 years.

Placebo arm: To calculate the probability of experiencing a first HE episode over 5 years in the placebo arm of the model, Norgine use data from trial RFHE3001 alone. Data was extrapolated by fitting a lognormal distribution to the 6-month study data. However the shape parameter from this regression was replaced by the shape parameter estimated from the lognormal distribution fitted to the combined dataset for the rifaximin arm. Figure 3 shows the two fitted curves for both arms.

Figure 3. Fitted curves to combined dataset (RFHE3001 and RFHE3002) for rifaximin arm and to RFHE3001 for the placebo arm in order to inform first breakthrough episode (lognormal distributions)



Two points in Norgine's approach are worth further discussion:

1. Use of the lognormal distribution:

   In their initial submission, Norgine only reported undertaking visual inspections of the fitted curves and using Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) to assess the best model fit. Although these are common steps in the assessment of fit process, they should not be the only ones used.

   Assessment of fit process should be undertaken in 4 steps:

   1. Assess the fit of the models to the observed curve. This step ensures internal validity and it consists in doing visual inspections and utilising approaches like the AIC and the BIC.
   2. Still to ensure internal validity, the observed hazard ratios from the original data should also be assessed. For example log-cumulative hazard plots and quantile-quantile plots should be used to assess the suitability of the proportional hazards and acceleration factor assumptions respectively.
   3. To ensure external validity, the plausibility of the extrapolated portion of the curves should also be assessed. This can be done, for example, by comparing the expected hazard over time with those predicted by the parametric models or by having an expert opinion to validate expected survival.
   4. Finally sensitivity analysis should be undertaken using alternative plausible models. This step should include the models that could potentially be a good fit to the data.

   Norgine followed the first step of the assessment process, but they felt short in following all the others. Even though sensitivity analysis using alternative models was presented, the models chosen were not appropriately justified.

   The lognormal distribution is an Accelerated Failure Time (AFT) model, which means that it measures the acceleration factor (or time ratio) across treatments. If a proportional treatment effect is assumed, then the AFT model requires there to be a constant time ratio. Norgine did not make any assumption regarding the proportionality of effect.

   The choice of the appropriate distribution is crucial in any type of survival analysis. In the case of Norgine's model, when other distributions were used to fit the data, the final ICER varied significantly in some cases. For example if the loglogistic distribution is used the ICER is £21,850 and using the Weibull distribution the ICER is £28,844 (compared with the original ICER of £23,186).

2. Use of the combined dataset in the rifaximin arm:

Using the combined dataset from the RFHE3001 and RFHE3002 studies in the rifaximin arm entailed some assumptions. Firstly this meant using different datasets to fit each treatment arm separately since for the placebo arm only RFHE3002 data was used.

Using different datasets to fit separate arms of the model may be justifiable if this adds value to the analysis by providing more accurate and rich data. Norgine approach to take the 2 years follow-up data for the rifaximin arm seems sensible as it takes advantage of all available data. Since the population in the follow-up study considered for the economic analysis were patients continuing rifaximin from trial RFHE3001, there is no risk of bias.

Furthermore, Norgine took the shape parameter from the regression ran to fit the data for the rifaximin arm and used it to replace the shape parameter estimated from the lognormal distribution fitted to the placebo arm. Changing the shape parameter in the lognormal distribution has a great impact on the curve. This means it could potentially lead to the incorrect estimation (upwards or downwards) of the effectiveness in the treatment arm.

Norgine deterministic sensitivity analysis reinforces this concern, as it reveals that by varying the values of the shape parameters, a considerable impact was shown in the final ICER.

Overt state to remission after first breakthrough

In both arms of the model patients are assumed to always go back to remission after their first episode of HE. This seems appropriate for Norgine's analysis as it only looks into episodic HE.

Remission to overt state (subsequent episodes)

One of the reasons for discontinuation of study therapy in RFHE3001 trial was that patients experienced a breakthrough HE episode. As a result, Norgine had to make some assumptions to model time to subsequent episodes, namely:

- The risk associated with experiencing a subsequent overt HE episode was considered to be independent of the risk of preceding episode(s).
- The risk of subsequent overt HE episodes was considered independent of time spent in the remission health state.
- The risk of subsequent overt HE episodes was assumed to be constant over time and the same risk reduction for the first breakthrough episode was applied to subsequent episodes.

Data on time to first breakthrough episode from RFHE3001 trial were used to model the probability of patients experiencing a subsequent HE episode. An exponential curve was fitted to the data. It should be noted that by fitting these data with an exponential curve (instead of a lognormal), the resulting coefficient parameters were used to inform the hazard ratio between

HE events across treatment arms, and not the difference in time to event across arms. The hazard ratio for rifaximin versus placebo was estimated and applied to the baseline survivor function (placebo) to estimate the survivor function for rifaximin.

It is our understanding that the underlying assumption of a constant probability of subsequent episodes over time is not necessarily reflective of reality as per consultation with our expert clinical advisor. This is contrary to what Norgine claims is their experts' opinion regarding this subject. As it is mentioned in Norgine' report, after a patient experiences one HE episode the likelihood of experiencing another, more severe episode increases with time.

From a more technical point of view, the use of the exponential distribution is also challengeable. In line with Norgine's assumptions the use of the exponential function implies that the hazard is likely to remain constant over lifetime and also proportional between treatment arms. However, visual inspection of the curves and the AIC and BIC values do not suggest a good fit to the data.

Overt state (subsequent episodes) to remission

In both arms of the model patients are assumed to always go back to remission after subsequent episodes of HE. This seems appropriate for Norgine analysis as it only looks into episodic HE.

- ### Mortality data

It is stated in the submission report that patients experiencing HE face higher mortality risk than those without the condition. Furthermore, the mortality risk is likely to increase further with more severe grades of HE. This means that rifaximin would potentially have an impact on overall survival by helping maintaining patients in remission. However, mortality data from study RFHE3001 were considered immature to capture the impact of rifaximin on survival.

The baseline mortality used in the model was a combination of all-cause mortality and HE specific mortality. Furthermore, since trial RFHE3001 did not include patients with more severe types of liver disease, other sources (Bustamante et al, 1999 and Shawcross et al, 2011) were used to capture mortality at the more severe end of the disease spectrum.

This approach is considered to be appropriate as it helped capturing mortality rates for a wider group of patients suffering from HE than those included in RFHE3001.

Calculation of all cause-mortality

Interim Life Tables for England and Wales (ONS) were used to obtain age and gender specific mortality rates, which were then converted into monthly probabilities. The data was adjusted to reflect the overrepresentation of males in the study population. The method used was considered appropriate.

Calculation of HE specific mortality in the remission state

Bustamante et al (1999) was used to model the increased mortality risk for liver disease patients compared with the general population. This study looked into the survival probability for patients with liver disease who had experienced a first episode of HE. A lognormal distribution was used to fit the data and extrapolate it over 5 years. Finally the different mortality risks were converted into time dependant transition probabilities over 5 years. The approach used by Norgine was considered to be generally good, even though the choice of the lognormal distribution was not justified thoroughly.

Calculation of HE specific mortality in the overt state

An overall weighted mortality risk was obtained by taking the proportion of patients within each Conn score category and attaching a mortality estimate to it. Conn score specific mortality rates were obtained through expert opinion and Shawcross et al (2011) (Based on the expert opinion sought by the ERG, the mortality assumed for the Conn score categories 3 and 4 might be an overestimate. If the mortality associated with these states was changed to reflect lower values, the overall mortality rate in the overt state would decrease, which would drive the final ICER upwards.

Table 20).

A small technical issue was found regarding this estimation. When calculating the weighted mortality risk for patients with different Conn scores, the total number of patients in the calculation did not add up to 100%. This had an impact on the overall mortality estimate. We have updated the results and the impact on model outcomes are presented in Section 6.1.2.

Based on the expert opinion sought by the ERG, the mortality assumed for the Conn score categories 3 and 4 might be an overestimate. If the mortality associated with these states was changed to reflect lower values, the overall mortality rate in the overt state would decrease, which would drive the final ICER upwards.

Table 20. Mortality rates by Conn score in the overt health state

Conn score	Estimate	Reference
1	5%	Assumption
2	20%	Clinician estimate
3	53.86%	Shawcross et al (2011)
4	71.89%	Shawcross et al (2011)

Mortality has a significant impact on the value of the final ICER. The fact that mortality rates associated with the overt and the remission state are different is a key driver of the difference in QALYs across treatment arms.

We can observe from Error! Reference source not found.

Figure 4 and Figure 5 that in a cohort of a 1,000 patients, after 5 years approximately 910 patients die in the placebo arm while approximately 900 die in the rifaximin group. This is due to the effect of rifaximin preventing the recurrence of HE events (i.e. moving to the overt category). Consequently, in the rifaximin arm, less people are exposed to the higher mortality rate associated with the overt state compared to the remission state.

Figure 4. Markov trace diagram – placebo

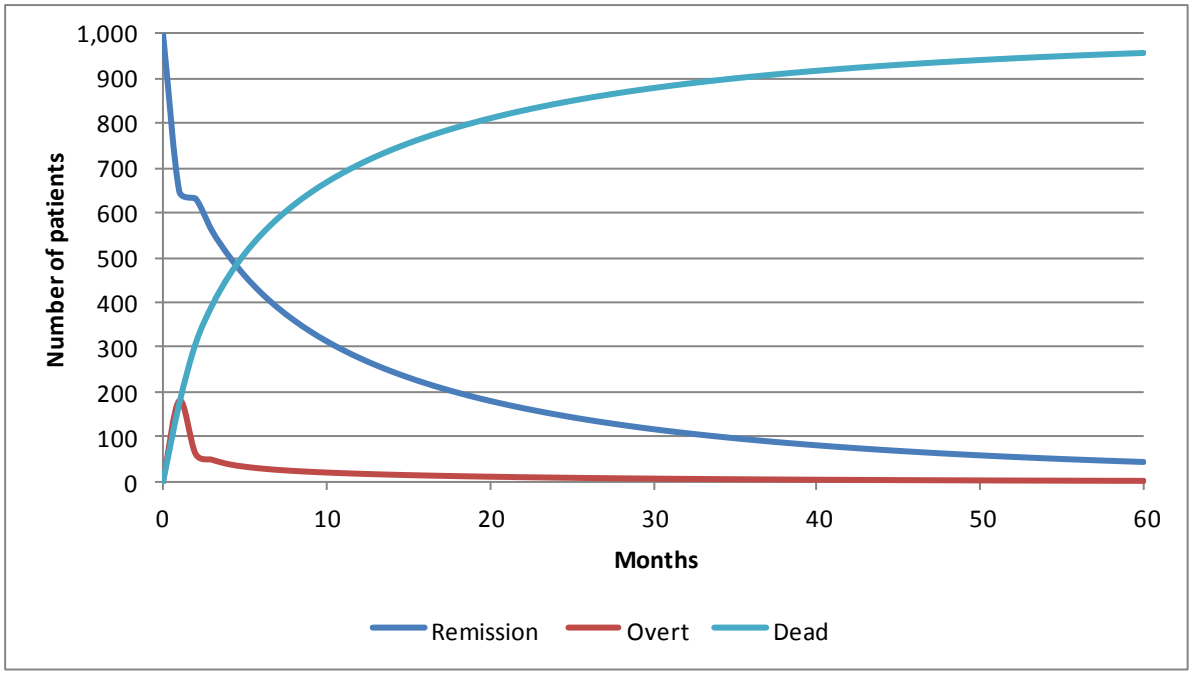
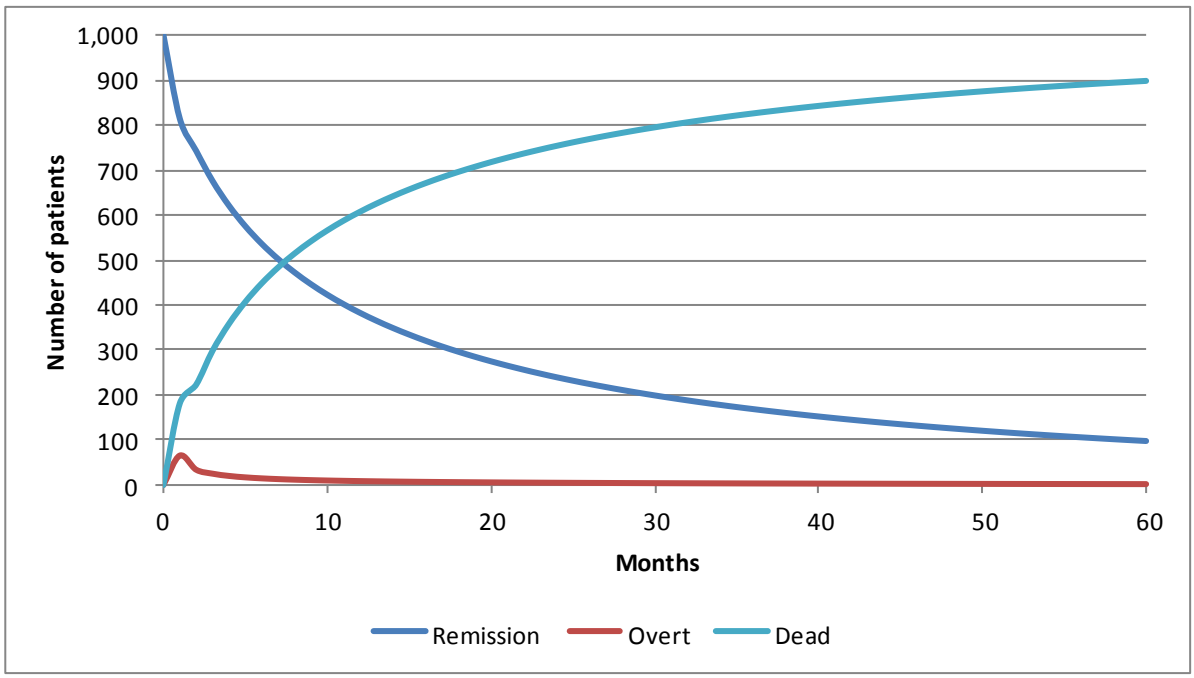


Figure 5. Markov trace - rifaximin



- ### Drug costs

Overall the calculation of drug costs in the model was satisfactory with the exception of one detail concerning the cost of lactulose. As mentioned in Section 5.1, not all patients in both arms of the trial took lactulose. In fact 91.4% and 91.2% of patients in the rifaximin and the placebo arm respectively were taking lactulose. This should have been accounted for in the calculation of lactulose total cost. The overall impact on the model outcomes is not major. The results are presented in Section 6.2.3 of the report.

- ### Disease management costs

No major issues concerning the computation of disease management costs were identified in the model. Resource use was entirely based on expert opinion however after consulting with our expert clinical advisor the values used by Norgine seem sensible.

- ### Adverse event costs

Norgine presented a detailed description of adverse events for each intervention group.

For study RFHE3001 Norgine considered that the proportions of patients experiencing adverse events were comparable between the rifaximin and placebo groups; therefore costs for adverse events were not calculated. However they did not present relative risks and risk difference and associated 95% confidence intervals for each adverse event, which would have provided a stronger case for their decision of not costing adverse events.

For study RFHE3002 Norgine indicated that adverse events that were considered to be related to study drug were recorded for [redacted] of subjects. Adverse events were not costed. [redacted], it is our understanding that cost and QALY calculations for these events would not have a significant impact on the final ICER.

- ### Health related quality of life

The preferred measure of HRQL in adults according to NICE is the EQ-5D. When EQ-5D data are not available or are considered to be inappropriate to capture the impact of the disease in patients' quality of life then the valuation methods should be fully described and compared to those used for the EQ-5D.

Despite expressing a clear preference for generic measures NICE recognises a role for condition-specific measures (CSM) as an alternative measure for quality of life. However CSM should not be used directly to undertake economic evaluations and should firstly be converted into a preference based measure. There are two approaches to do this: direct valuation and mapping.

The utilities used in the economic model were elicited as CSM in a study commissioned by Norgine. The study was undertaken among a sample of 200 randomly selected members of the general public at different locations across Greater London, UK and aged between 35 and 65 years of age. Participants were given a short description of HE and the five different health states according to the Conn score (grade 0,1,2,3 and 4). Then using the TTO method patients were asked what proportion of their remaining lifetime they would be willing to sacrifice in return for not living with the symptoms associated with each of the health states described. After obtaining the utility values for the five different health states, regression analysis was undertaken to assess the relationship between baseline variables (such as age, gender, income, etc) associated with each health state and the preference values.

Norgine chose the direct valuation method to convert the CSM into preference based measures. This process usually entails the following steps:

1. Item selection
2. Generation of health states
3. Preference elicitation
4. Estimation of model to value all relevant health states (usually done by using multi-attribute utility theory or alternatively undertaking statistical inference)
5. Validation of model performance

Norgine's submission report does not provide details on some of the steps mentioned above. The utility study provided by Norgine reported the statistical inference undertaken, even though it seems that no validation of the model performance was performed.

The mean utilities (95% CI) derived for HE health states are presented in Table 21.

Table 21. Mean utilities (95% confidence intervals) for HE by Conn score

	Conn score 0	Conn score 1	Conn score 2	Conn score 3	Conn score 4
Whole cohort (using TTO)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Whole cohort (using SG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Finally to obtain the utilities for the three health states of the economic model (presented in Table 13), Norgine used the mean utilities reported in Table 21 and weighted these by the percentage of patients in each Conn score category in the overt and in the remission states.

Some technical issues were found in Norgine's estimation of utility values specific to the overt health state:

- When calculating the weighted utility score for patients with different Conn scores, the total number of patients in the calculation did not add up to 100%. This had an impact on the overall utility estimate. We have updated the results and the impact on model outcomes are presented below in Section 6.1.2
- Utility calculations were a case in the model where the cycle length was not clear. A 28 day cycle was originally used by Norgine for estimating the utility in the overt state. This is better explained by the following formula which describes how the overt utility value was calculated:

  Overt state utility value = utility for remission * time spent in remission + utility for HE episode * time spent experiencing HE episode

We modified the total cycle length so that it would add up to 30.4 days. The impact on the economic outputs is presented in Section 6.1.2

5.2.4 Sensitivity analysis

A range of one-way deterministic sensitivity analysis was provided in Norgine's submission. A tornado diagram was generated to demonstrate the effect of varying some of the individual parameters in the model (Submission p.129).

One-way sensitivity analysis covered parameter uncertainty by varying the values used in the model by their upper and lower confidence interval values (95%CI) and structural uncertainty by using different data to model some of the parameters.

In addition to deterministic sensitivity analysis, Norgine also presented PSA. Parameters' uncertainty was represented by using probabilistic distributions and Monte Carlo simulations.

5.3 Results included in manufacturer's submission

This section presents a summary of the results of Norgine's model. See Section 7.7 of Norgine's submission for further details. The results in this section are as they appear in Norgine's submission.

5.3.1 Deterministic results

- Base case

Base case outputs produced by the economic model are present in
Table 22.

Table 22. Base case outputs per patients at 60 months

Cost-effectiveness results per patient	Rifaximin + lactulose (1)	Lactulose + placebo (2)	Incremental value (1-2)
Total costs £	£5,168.21	£820.71	**£4,347.50**
QALYs	1.2179	1.0304	**0.1875**
Survival (Bustamante)	10%	6%	**4%**
ICER			**£23,186**

Source: Adapted from Submission. Table 50, p128 and Norgine reply to ERG request for clarification.

Norgine also undertook two subgroup analyses, one for patients receiving concomitant lactulose in both arms of the model (subgroup A) and other for patients not receiving lactulose (subgroup B). Subgroup A and B represent 91.3% and 8.7% of the ITT population in study RFHE3001, respectively.

These subgroups were not a pre-planned subgroup analysis in the clinical trial, hence the analysis was based directly on evidence from study RFHE3001 in which 91.4% of patients in the rifaximin arm and 91.2% in the placebo arm received concomitant lactulose, respectively. Post-hoc analyses were not formally undertaken.

Particular caution should be taken when interpreting these results, especially due to the small sample size in subgroup B. Nonetheless, we found this analysis informative to some extent. Results from the base case in the subgroup analysis are presented in Table 23 and

Table 24.

Table 23. Subgroup A results – 100% concomitant lactulose use (91.3% of the ITT population)

Cost-effectiveness results per patient	Rifaximin + lactulose (1)	Lactulose + placebo (2)	Incremental value (1-2)
Total costs £	£5,044.21	£826.25	**£4,217.96**
QALYs	1.1771	1.0136	**0.1635**
ICER			**£25,785**

Source: Adapted from Submission. Table 50, p140.

Table 24. Subgroup B results – 0% concomitant lactulose use (8.7% of the ITT population)

Cost-effectiveness results per patient	Rifaximin (1)	Placebo (2)	Incremental value (1-2)
Total costs £	£5,356.89	£599.79	**£4,757.1**
QALYs	1.2323	1.1011	**0.1312**
ICER			**£36,254**

Source: Adapted from Submission. Table 50, p.141.

- ## One-way sensitivity analysis

We found the analysis to be confusing not only when reported but also in the Excel model. Labelling was not clear. Also some parameters seem to have been left out, more specifically the exponential regression parameters used to model the subsequent HE episodes and the lognormal constant parameter used to model time to first HE episode in the placebo arm, were not included in one-way sensitivity analysis. In Section 6 of the report we present the results for the one-way sensitivity analysis including these parameters.

Table 25 summarises the results reported by Norgine. The outputs from the one-way sensitivity analysis show that the model is most sensitive to changes in the lognormal estimates used to estimate the transition probabilities.

Table 25. One-way sensitivity analysis parameters and outcomes

Variable	CE with low value (ICER)	CE with high value (ICER)	Difference in the ICER
Lognormal regression constant parameter (ITT) (first breakthrough episode) (1.67 to 2.47; base case 2.07)[4]	£20,345	£27,101	£6,756
Lognormal regression constant parameter (ITT combined dataset) (rifaximin) (4.64 to 3.39; base case 4.01)	£27,121	£20,550	£6,571
Lognormal regression constant parameter (mortality) (2.35 to 1.60; base case 1.98)[4]	£21,872	£24,459	£4,095
Lognormal regression /ln_sig paramter (mortality) (0.82 to 0.51; base case 0.67)	£23,841	£22,151	£3,861

[4] This parameter was not used in the economic model. It should not have been reported in the sensitivity analysis.

Variable	CE with low value (ICER)	CE with high value (ICER)	Difference in the ICER
Lognormal regression /ln_sig paramter (ITT) (first breakthrough episode) (0.54 to 0.86; base case 0.70)	£23,724	£22,110	£2,587
Lognormal regression /ln_sig parameter (ITT combined dataset) (rifaximin) (0.81 to 1.22; base case 1.02)	£24,303	£22,906	£2,118
Duration of episode (utility) - lactulose (28 to 1; base case 11)	£23,658	£22,732	£1,690
Length of stay (placebo) (11 to 2; base case 5)	£22,886	£23,785	£1,614
Frequency of outpatient visits (6 to 1; base case 3)	£22,929	£23,636	£1,397
TTO utility for Conn Score 0 (0.99 to 0.94; base case 0.96)	£23,517	£22,864	£926
Length of stay (rifaximin)	£22,886	£23,785	£899
Duration of episode (utility) - rifaximin	£22,929	£23,636	£707
TTO utility for Conn Score 1	£23,517	£22,864	£654
Percentage hospitalised - placebo + lactulose (ITT)	£23,454	£22,858	£596
Percentage hospitalised - rifaximin + lactulose (ITT)	£22,984	£23,451	£467
TTO utility for Conn Score 2	£23,131	£23,241	£111
TTO utility for Conn Score 3	£23,157	£23,215	£57
Non-Malignant Liver Disorders without Major CCs	£23,194	£23,178	£15
Non-Malignant Liver Disorders with Major CCs	£23,190	£23,181	£9
TTO utility for Conn Score 4	£23,182	£23,190	£8
Average daily dose of lactulose - rifaximin arm	£23,182	£23,190	£8
Average daily dose of lactulose - placebo arm	£23,190	£23,182	£8
Non-Malignant Liver Disorders with Severe CCs	£23,188	£23,184	£5
Non-Malignant Liver Disorders with Catastrophic CCs	£23,188	£23,184	£5
Liver Failure Disorders without Interventions	£23,188	£23,184	£4
Liver Failure Disorders with Interventions	£23,187	£23,185	£2
Cost of outpatient visit	£23,186	£23,186	£1

Adapted from Submission. Figure 21, p.129 and Norgine model (Excel).

Structural uncertainty was addressed using a number of scenarios. The main results are presented in Table 26.

Some of the choices of alternative parameters were not justified. This was the case for the choice of the exponential, Gompertz and Weibull distributions as alternatives for the lognormal distribution. The ERG asked Norgine why these distributions were selected to undertake

sensitivity analysis, to which Norgine replied that this was a way of showing results based on the proportional hazards metric.

This justification raises some questions. As explained before, the lognormal model is an AFT model which means that it measures the acceleration factor (or time ratio) across treatments. When using the exponential or the Gompertz model, it is assumed that the hazard risk between treatment and control arms has some relationship (being proportional or not). So the assumption these entail (note that the Weibull can be parameterised as an AFT or a proportional hazard model) are quite different. While the lognormal model assesses how fast one specific outcome (in this case HE episode) occurs in the treatment arm compared with the control, the exponential and Gompertz models assess the relationship between the proportion of events in both arms.

We estimated that using the loglogistic distribution, which potentially is more suited for comparison with the lognormal, the final ICER value would be of £21,850.

More importantly, the use of the exponential distribution to model subsequent HE episodes was not explored in anyway throughout Norgine's analysis. This is a concern as the assumptions underlying the analysis are questionable. We explore this topic in Section 6.1.3.

Table 26. Scenario analysis

Variable in the model	Alternative used	ICER	Difference in ICER (base case – alternative)[5]
Lognormal distribution used to estimate time to first HE episode	Exponential	£15,032	£8,154
	Gompertz	£14,311	£8,875
	Weibull	£28,844	-£5,658
Addition of all-cause mortality to liver disease related mortality	Exclusion of all-cause mortality to account for possible double counting	£23,012	£174
Using age-adjusted utility values	Removing age-adjustment utility values	£23,186	£0
Generic preference based measure of QoL was used to estimate QALYs. TTO method was used.	Using SG method	£24,439	-£1,253

[5] ERG calculation

Variable in the model	Alternative used	ICER	Difference in ICER (base case – alternative)[6]
	Using other utility values (Wong et al, 1998)	£26,431	-£3,245
Percentage of patients falling within each Conn score category at first HE episode: • Conn score 1: 16% • Conn score 2: 52% • Conn score 3: 22% • Conn Score 4: 3%	Percentage of patients falling within each Conn score category at first HE episode: • Assumed to be 25% across all categories	£17,155	£6,031
Base case analysis assumed 100% compliance	Rifaximin compliance: 84.3% Placebo compliance: 84.9% As to reflect the overall rate of compliance in the clinical trial.	£19,599	£3,587

Adapted from Norgine Submission pp.133 – 135.

5.3.2 Probabilistic sensitivity analysis results

The cost-effectiveness acceptability curve (CEAC) presented by Norgine is shown in Figure 6. The results demonstrate that at a willingness-to-pay threshold value of £30,000 per QALY the probability of rifaximin plus concomitant lactulose being cost-effective when compared to placebo plus concomitant lactulose is 99.60%.

The cost effectiveness plan was also reported (Submission p131).

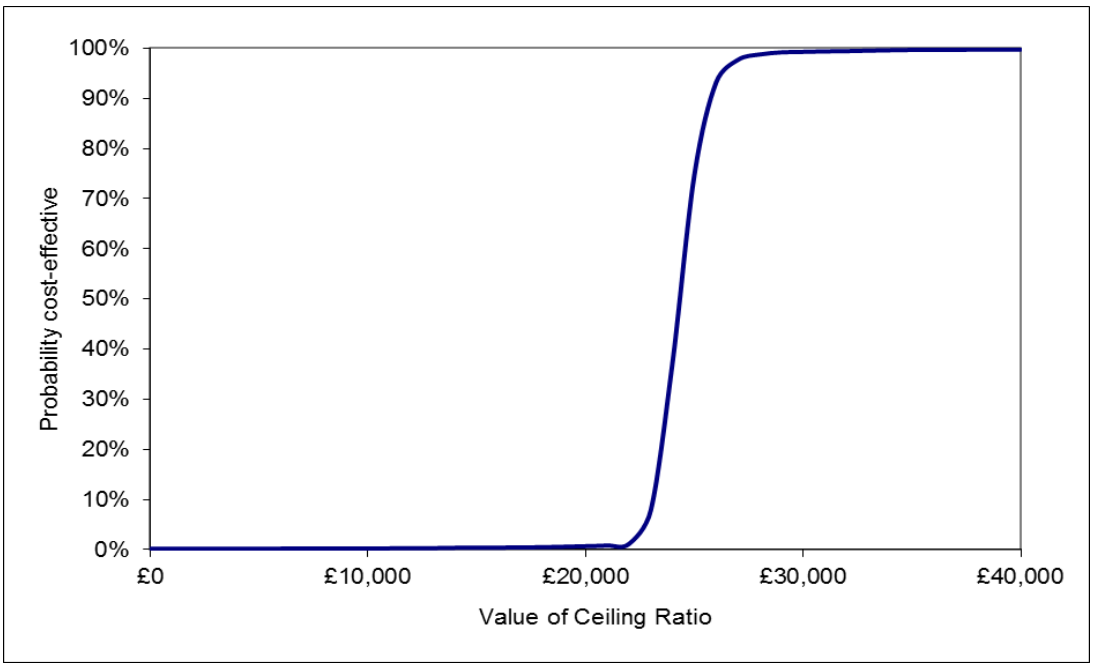
Results and implications from PSA were not fully explored in the report. Again we found this analysis confusing in the Excel model. Labelling was not clear. Also some parameters seem to have been left out, more specifically the exponential regression parameters used to model the subsequent HE episodes and the lognormal constant parameter used to model time to first HE episode in the placebo arm, were not included in one-way sensitivity analysis.

Furthermore we found a linking mistake in the Excel model. This had an impact on the probabilistic parameters in the lognormal distribution used to model time to first breakthrough in the rifaximin arm. The method used by Norgine to assess uncertainty around these parameters consisted in employing the Cholesky decomposition to provide correlated draws from a multivariate normal distribution. We address the impact of this correction in Section 6.

Superseded - see erratum

[6] ERG calculation

Figure 6: Cost-effectiveness acceptability curve



Source: Submission Figure 23, p. 133.

5.4 Comment on validity of results presented with reference to methodology used

5.4.1 Modelling approach and structure and data inputs

In Sections 5.2.2 and 5.2.3 we provided a detailed description of the modelling approach and structure adopted by Norgine and of the data and estimations used to populate the model.

The **approach and structure** of the model was found appropriate to the decision problem, and generally in line with the scope. However, it is important to mention three key deviations from the scope:

- **Population**. The analysis refers to adults with chronic liver disease who have had prior episodes of overt HE and are currently in remission. Also patients with more severe liver disease (MELD score ≥25) were excluded from the analysis. Therefore, the indication and submission do not cover patients with HE caused by an acute liver insult and patients with more severe liver disease.
- **Intervention**. Although in the scope the intervention was specified as rifaximin, in the study used for the submission 91.3% of the patients were using concomitant lactulose. This reflects current practice. However, for patients not receiving lactulose (8.7%) the ICER is £36,254 per QALY and due to the small sample size is potentially subject to

- large variability. Therefore, if the indication of rifaximin is meant for patients taking rifaximin alone, then the economic model developed by Norgine for this submission is not sufficient to inform the overall costs and benefits of the drug.
- **Comparators**. The comparator used in the analysis is placebo plus concomitant lactulose. Neomycin and neomycin with lactulose were not used as comparators.

With regards **data inputs**, wherever relevant we flagged the calculation errors found. We also challenged a number decisions and assumptions made in the analysis, in particular with regards the extrapolation of effectiveness data.

Here we list aspects that needed our attention, more specifically points where the ERG has undertaken additional work (presented in Section 6) or that need discussing.

- Cycle length
- Proportion of patients allocated to each Conn score category
- Cost of lactulose
- Exclusion of neomycin as a comparator
- Constant probability of subsequent HE episodes

These are explored in Section 6.

5.4.2 Assessment of consistency

- #### Internal consistency

We have checked the mathematics, statistics, internal logic and implementation of the model in Excel, as well as results presented by Norgine. We identified some small technical errors, as described in previous sections. In Section 6 we present results with the corrections made.

- #### External consistency

We agree with Norgine's assertion that it is difficult to compare the results of their model with other models are there is a lack of published economic literature on the use of rifaximin for the prevention or treatment of HE.

The systematic review of the literature identified three potentially relevant economic evaluations (Huang et al, 2007; Bajaj et al, 2012; Paul et al, 2012) but these were not considered to be relevant as the patient population and outcomes do not match that of the current decision problem.

5.4.3 Assessment of uncertainty

The ERG found the following issues to be the key concerns in terms of potential uncertainty around the final ICER:

Superseded - see erratum

- Based on clinical expert opinion, the mortality rates associated with Conn scores 3 and 4 used in the model may represent an overestimate. If this was the case, then replacing these values by lower mortality rates would drive the ICER upwards, as there would be less QALYs gained due to the reduction of HE events associated with rifaximin. Even though the parameters associated with the transition probabilities to the death state have been tested in sensitivity analysis, we believe this may not fully capture the uncertainty in the mortality data available to the submission.
- Sensitivity analysis of the effectiveness of rifaximin was not fully assessed. Norgine undertook sensitivity analysis of the parameters associated with the rifaximin arm but the parameters associated with the placebo arm were not tested in sensitivity analysis.
- Subsequent HE episodes were modelled with a constant probability, and this was not assessed in sensitivity analysis.

6.0 Additional work undertaken by the ERG

In this section we explore the implications of the errors found in Norgine's model. We have made a distinction between technical and conceptual errors. In Section 6.2.1 we explain our approach to deal with the errors and where possible in Section 6.2.2 we present the implication of these with regards to model outputs. Finally we report one-way sensitivity analysis.

6.1.1 Correction for errors in Norgine's model

After identifying some technical errors, we have made the following adjustments to Norgine's base case model:

1. It was not clear in the manufacturer's report what the model cycle length used was. The same issue was present in Norgine's economic model where the cycle length was sometimes considered to be 28 days and others 30.4 days. For the sake of consistency we have updated all values in the economic model so that the cycle length in every parameter calculation reflected a month duration of 30.4 days.

2. In order to calculate utility values and mortality rates, Norgine used the percentage of patients within each Conn score category. However the total percentage of patients did not add up to 100%. This was due to lack of information on the Conn score for HE episodes in all patients (for example, 7 patients in the placebo arm of the model did not have available information on the Conn score associated with their HE episode). We have reweighted this, so that the total population adds up to 100%.

3. Not all patients in both arms of the trial took lactulose. In fact 91.4% and 91.2% of patients in the rifaximin and the placebo arm respectively were taking lactulose. We took this into account for the calculation of lactulose total cost.

We have also explored alternative scenarios to deal with some of the conceptual issues in Norgine's model:

1. Norgine made a decision to exclude neomycin from the analysis as a comparator. Although we find plausibility in some of the reasons provided for this decision there is value in presenting some key information for neomycin, in particular given that one study (Miglio et al, 1997) found rifaximin and neomycin were equally effective in reducing HE grade after 30 days.

   Therefore, we replaced the cost of rifaximin by the cost of neomycin in Norgine's economic model. The cost and dose indication of neomycin were taken from the BNF. Neomycin sulphate for hepatic coma should be provided up to 4g daily in divided doses. The price for neomycin sulphate tablets 500mg (100 tablets) is £20.36. This adds up to 36/100x8 = £1.63 per day. We have also assumed the treatment would last 6 days per month.

Superseded - see erratum

2. As per consultation with our expert clinical advisor, the underlying assumption of a constant probability of subsequent HE episodes over time is not necessarily reflective of reality. The decision to use the exponential distribution to model this parameter was also not justified by Norgine.

   It was not possible to access the impact on the ICER of changing the assumption of constant probability of subsequent HE episodes over time. However, in order to assess Norgine's assumption, we analysed the data provided by Norgine (upon request of the ERG) which provides detail on time to first and subsequent episodes at individual level for patients in the RFHE3002 study.

3. We found the one-way sensitivity analysis to be confusing not only when reported but also in the Excel model. Some parameters were left out. More specifically, the lognormal constant parameter used to model time to first HE episode in the placebo arm and the exponential regression parameters used to model the subsequent HE episodes, were not included in one-way sensitivity analysis. We have included these parameters in the sensitivity analysis and re-run it.

4. We have corrected the linking error in the PSA parameters related with the Cholesky decomposition for the lognormal constant and shape parameters used to model time to first HE episode.

The impact of these changes is presented in Section 6.1.2 and Section 6.1.3.

6.1.2 Corrected base case outputs

With the changes explained in the previous section, Norgine's base case outputs changed as reported in

Table 27.

Table 27. Base case results with corrections from Norgine's model

Cost-effectiveness results per patient	Rifaximin + lactulose (1)	Lactulose alone (2)	Incremental value (1-3)
Base Case			
Total costs £	£5,168.21	£820.71	**£4,347.71**
QALYs	1.2179	1.0304	**0.1875**
ICER			**£23,186**
Cycle length correction			
Total costs £	£5,168.21	£820.71	**£4,347.71**
QALYs	1.2202	1.0361	**0.1841**
ICER (compared with base case)			**£23,613**
ICER with all changes incorporated			**£23,613**
Proportion of patients allocated to each Conn score category correction			
Total costs £	£5,124.25	£802.55	**£4,321.70**
QALYs	1.2084	0.1971	**0.1875**
ICER (compared with base case)			**£21,929**
ICER with all changes incorporated			**£22,299**
Cost of lactulose correction			
Total costs £	£5,159.48	£812.21	**£4,347.28**
QALYs	1.2179	1.0304	**0.1875**
ICER (compared with base case)			**£23,185**
ICER with all changes incorporated			**£22,298**

6.1.3 Additional analysis undertaken by the ERG

Cost-effectiveness of neomycin

Miglio et al (1997) found rifaximin and neomycin were equally effective in reducing HE grade after 30 days. Assuming that neomycin would have the same effectiveness as rifaximin in terms of reducing breakthrough HE episodes compared with placebo, we estimated the corresponding ICER for neomycin.

Since neomycin is considerably cheaper than rifaximin, the results show the ICER for neomycin plus concomitant lactulose compared to lactulose is much lower than the ICER for rifaximin plus concomitant lactulose compared to lactulose. This suggests that in patients that respond to neomycin, this represents a more cost-effective alternative than rifaximin.

Table 28. Cost-effectiveness of neomycin (assuming same effect as rifaximin)

Cost-effectiveness results per patient	Neomycin + lactulose (1)	Lactulose alone (2)	Incremental value (1-3)
Total costs £	£950.55	£820.71	**£129.84**
QALYs	1.2179	1.0304	**0.1875**
ICER for neomycin			**£692.48**

Constant probability of experiencing subsequent HE episodes assumption

Using data provided by Norgine, we looked into [redacted] patients from study RFHE3002 who experienced one or more HE episodes over 2 years. Table 29 shows the data for up to 8 subsequent episodes. We also present the total time to episodes and the average time per patient.

[redacted]

[redacted]

[redacted].

[redacted] Although the impact on the final ICER is not easily foreseen, it is important to flag Norgine's assumptions as a potential driver for uncertainty in the estimated ICER.

Table 29. Time to episode for patients in RFHE3002 study

Episode	Number of patients	Proportion of patients with subsequent episodes	Total time to episodes (days)	Average time per patient
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

One-way sensitivity analysis

Since our technical corrections to the model made little impact on the final ICER, re-running one-way sensitivity analysis for all the parameters would not be of much value. However, as mentioned before, some parameters were left out from Norgine's original one-way sensitivity analysis. More specifically the exponential regression parameters used to model the subsequent HE episodes and the lognormal constant parameter used to model time to first HE episode in the placebo arm were not included in the one-way sensitivity analysis. We therefore ran sensitivity analysis for these parameters. The results are presented in Table 30.

The impact of varying these parameters by their lower and upper 95% CIs was not major, with the lowest ICER being £20,345 and the highest £26,105.

Table 30. One-way sensitivity analysis with added parameters

Cost-effectiveness results per patient	Incremental cost	Incremental QALY	ICER rifaximin vs. placebo
Base case	£4,347.71	0.1875	**£23,186**

Lower 95% CI for lognormal constant parameter used to model 1st HE episode in placebo arm	£4,340.19	0.2133	**£20,345**
Upper 95% CI for lognormal constant parameter used to model 1st HE episode in placebo arm	£4,340.19	0.2133	**£26,105**
Lower 95% CI for exponential treatment parameter used to model subsequent HE episodes	£4,395.21	0.2028	**£21,675**
Upper 95% CI for exponential treatment parameter used to model subsequent HE episodes	£4,285.30	0.1678	**£25,544**
Lower 95% CI for exponential constant parameter used to model subsequent HE episodes	£4,377.70	0.1708	**£25,626**
Lower 95% CI for exponential constant parameter used to model subsequent HE episodes	£4,313.05	0.2040	**£21,138**

Probabilistic sensitivity analysis

The submission reports an ICER of £23,373 (CI: £21,500 to £26,048) resulting from PSA. Our correction of the cells linked to the PSA parameters, suggests that the final ICER may vary across a wider range than the one reported by Norgine.

7.0 Summary of clinical and cost-effectiveness issues

- It is likely that the clinical systematic review of the literature undertaken by Norgine contains all the relevant studies.
- The submitted evidence reflects the decision problem adequately, even though it departed from NICE original scope, especially in terms of population and comparators covered.
- The evidence is based on only one completed and published RCT (RFHE3001). The follow-up study (RFHE3002) is an unpublished long-term evaluation of the safety and tolerability of rifaximin, and does not provide treatment effect data.
- The manufacturer's submission summarised the identified benefits as:
    - Rifaximin 550 mg twice a day plus lactulose significantly reduced (p<0.001) the relative risk of recurrence of overt HE episodes by 58% (hazard ratio 0.42, 95% confidence interval (CI), 0.28 to 0.64) vs. placebo plus lactulose over 6 months.
    - Rifaximin 550 mg twice a day plus lactulose significantly reduced (p=0.01) the relative risk of hospitalisation involving HE by 50% (hazard ratio 0.50, 95% CI, 0.29 to 0.87) vs. placebo plus lactulose over 6 months.
    - Norgine indicated that the incidence and seriousness of adverse events reported during the study was similar between the rifaximin and placebo groups. However they did not present relative risks and risk difference and associated 95% confidence intervals for each adverse event, which would have provided a stronger case for their decision of not costing adverse events.
    - RFHE3002 showed that long term treatment over 24 months with rifaximin 550 mg twice a day plus lactulose provided continued protection from HE and reduced the hospitalisation rate.
- Mortality data from trial RFHE3001 was considered not to be mature enough to capture the drug overall impact on survival. However the model captures the effect of rifaximin vs. placebo on mortality by reducing the recurrence of HE events, and the increased mortality rate associated these events.
- A number of decisions in the extrapolation of data from studies RFHE3001 and RFHE3002 were not appropriately justified.
- The underlying assumption of a constant probability of subsequent HE episodes over time was not validated by our expert.
  [redacted]
- Several parameters in the model were estimated solely based on expert opinion.
- In their economic evaluation, Norgine presented some minor errors. After correcting for all errors, the final ICER is £22,298 per QALY (compared to £23,186 reported by Norgine).
- For patients not receiving lactulose (8.7%) the ICER is £36,254 per QALY and due to the small sample size is potentially subject to large variability. Therefore, if the indication of rifaximin is meant for patients taking rifaximin alone, then the economic model developed by Norgine for this submission is not sufficient to inform the overall costs and benefits of the drug.

8.0 References

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