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

A critique of the submission from Norgine

Erratum

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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.

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Contribution of authors

Mariana Bacelar: Contributed to the critique of the manufacturer's submission, report writing and editing.

Evelina Bertranou: Contributed to project management, the critique of the manufacturer's submission, report writing and editing.

Chris Cooper: Commented on the searches provided by the manufacturer and contributed to report writing.

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Contents

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the location of the change in the original ERG report and the nature of the change.

Page no.	Change
7	Given that not all 100% of patients in the comparator used lactulose, the manufacturer has requested that 'comparator used was placebo plus concomitant lactulose' is replaced with 'comparator used was placebo'.
10	As above.
12	As above.
13	Based on RFHE3002 follow-up study, the manufacturer has requested that 'There are no equivalent studies assessing the long-term use of rifaximin and its side effects' is excluded from the section comparing neomycin and rifaximin.
27	Given that not all 100% of patients in the comparator used lactulose, the manufacturer has requested that 'comparator used was placebo plus concomitant lactulose' is replaced with 'comparator used was placebo'.
66	Replaced one-way sensitivity analysis with sensitivity analysis
68	Given that not all 100% of patients in the comparator used lactulose, the manufacturer has requested that 'comparator used was placebo plus concomitant lactulose' is replaced with 'comparator used was placebo'.
70	Corrected formula for price of neomycin

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.

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.

- 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. 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.

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. 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.

[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.	As mentioned above, Neomycin is still sometimes used by certain groups of patients, even if for shorter periods of time.
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.

1.1 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.

1.2 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.

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. Neomycin and neomycin with lactulose were not used as comparators.

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

5.3.2 Probabilistic sensitivity analysis results

The cost-effectiveness acceptability curve (CEAC) presented by Norgine is shown in **Error! Reference source not found.**. 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 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.

- 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. 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:

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 20.36/100x8 = £1.63 per day. We have also assumed the treatment would last 6 days per month.