Norgine response to NICE Technology Appraisal Committee's request for further analysis on Rifaximin-α 550mg

A Critique of the revised data submitted by Norgine

March 2014

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Executive summary

The original submission from Norgine Pharmaceuticals considered the use of rifaximin-α (Targaxan®) for the reduction in the recurrence of episodes of overt hepatic encephalopathy (HE). 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 Committee considered whether rifaximin reflected a cost-effective use of NHS resources. After considering the original submission, the Committee concluded that the ICER resulting from the analysis was not plausible based on the uncertainties around model parameters and assumptions.

Norgine submitted an addendum to their original submission. The Committee noted that the manufacturer's base-case ICER was £20,799 per QALY gained for rifaximin plus lactulose compared with placebo plus lactulose. After considering the updated submission, the Committee concluded that the ICER resulting from the analysis was not plausible based on the uncertainties around model parameters and assumptions.

The uncertainties in Norgine's updated analysis related to the following matters:

- A 5 year time horizon was used in the economic model. This was considered inappropriate for the purpose of capturing all the relevant costs and benefits associated with rifaximin. The Committee suggested that a lifetime time horizon was employed in the economic analysis.
- Norgine used SF-36 observations collected in RFHE3001 to map to EQ-5D utility values however further analysis was undertaken to establish the relationship between CLDQ scores and the estimated EQ-5D index utility generated from the mapping exercise. Introducing further modelling steps after the mapping exercise to quantify the relationship with CLDQ scores was considered unnecessary and deemed to introduce further uncertainties in the analysis.
- The submitted model predicted a difference of 3.6% in the risk of mortality with rifaximin compared with placebo during the first 6 months of the model and a difference of up to 8% over the 5-year time horizon. This was considered to be unreflective of clinical reality, where a diminishing benefit mortality would be expected over time.
- The Committee requested that a full probabilistic sensitivity analysis was undertaken for the revised analysis, including the probabilistic ICERs.

Following the NICE appraisal consultation process in October 2013, Norgine have submitted additional evidence and a revised cost-effectiveness model. Revision of the additional evidence suggests that:

- The economic results are more robust when a lifetime time horizon is used as costs and benefits are appropriately captured.
- When the revised utility data and the lifetime time perspective are considered simultaneously in the economic analysis, the final base case ICER is **£28,805** per QALY.
- The revised utility values used in the economic analysis are a source of concern to the ERG:
    - The difference in utility assumed between rifaximin and placebo was derived using the adjusted utility analysis, however the ERG are concerned with the lack of detail and the validity of the analysis.
    - The utility value associated with the covert state in the placebo arm of the model is not sourced.
    - The difference in utility assumed between the covert and the overt states in the model comes from the manufacturer's original submission, where utility values were taken

from a study commissioned by Norgine and health state preferences were derived from the general public.

- The key driver of the cost-effectiveness results is the revised incremental utility assumed for rifaximin patients in the covert state compared with placebo patients in the covert state. The method used to derive such estimates raises some concerns. Therefore it is strongly recommended that clinical opinion is used to validate the utility gains claimed by the manufacturer.
- The incremental mortality benefit associated with rifaximin treatment compared with placebo is now in agreement with clinical reality as a diminishing benefit is observed over time. Furthermore, mortality is not likely to be a key driver of the final ICER and the modelled values are generally in accordance with real life data.
- Probabilistic sensitivity analysis showed that the revised utilities values used in the model are key drivers of the final ICER.

1.0 Introduction

The original submission from Norgine Pharmaceuticals 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 Committee considered whether rifaximin-α (hereafter referred to as rifaximin) reflected a cost-effective use of NHS resources. After considering the original submission, the Committee concluded that the ICER resulting from the analysis was not plausible based on the uncertainties around model parameters and assumptions.

Norgine submitted an addendum to their original submission. The Committee noted that the manufacturer's base-case ICER was £20,799 per QALY gained for rifaximin plus lactulose compared with placebo plus lactulose. After considering the updated submission, the Committee concluded that the ICER resulting from the analysis was not plausible based on the uncertainties around model parameters and assumptions.

Following the NICE appraisal consultation process in October 2013, Norgine Pharmaceuticals were requested to submit additional analyses in relation to the appraisal of rifaximin for the reduction in the recurrence of episodes of HE in patients 18 years of age and older.

This document presents a critique of the additional evidence and the revised cost-effectiveness model submitted by Norgine in the Response to NICE Technology Appraisal Committee's Request for Further Analysis (hereafter referred to as the revised analysis) as a response of the concerns highlighted by the Committee.

The remainder of this report is structured as follows:

- Section 2 reviews the lifetime time horizon adopted.
- Section 3 reviews the new utility values used in the revised model.
- Section 4 reviews the additional evidence relating to mortality.
- Section 5 refers to the results of the economic model.
- Section 6 concludes.

Where relevant, the sections introduced above are organised as follows:

- Summary of previous submission and Committee's comment
- Overview of method applied in the revised analysis
- Critique of the method applied in the revised analysis
- Implications

2.0 Lifetime perspective

Summary of previous submission and Committee's comment

In the addendum to their original analysis, the manufacturer presented base case ICERs over a period of 5 years and also alternative ICER estimates adopting a 10-year time perspective.

The Committee discussed the appropriateness of the 5-year time horizon used in the model. It noted that 52% of people in the rifaximin group and 45% in the placebo group were predicted as being still alive in the model after 5 years (ACD, section 4.6).

The Committee concluded that the manufacturer's choice of a 5-year time horizon was not in line with the NICE reference case and that a lifetime time horizon would be more appropriate to capture all relevant costs and benefits. It recommended that further analyses using a lifetime time horizon be requested (ACD, section 4.6).

Overview of method applied in the revised analysis

Norgine adopted a lifetime perspective for their economic analysis, where patients were followed for 42 years. By this time 100% of patients were virtually dead.

Critique of the method applied in the revised analysis

The ERG is satisfied with the approach taken. The time frame adopted is appropriate to capture all relevant costs and benefits resulting from the economic analysis.

Implications

Norgine reported a final base case ICER of £17,834 after a lifetime horizon had been adopted. However the ERG found a small mistake in the model. After correcting this, the final lifetime ICER decreased to £17,681.

Table 1. Lifetime ICER

Cost-effectiveness results per patient over lifetime	Rifaximin (1)	Placebo (2)	Incremental value (1-2)
Total costs £	£28,874	£6,925	£21,949
QALYs	4.452	3.211	1.241
ICER			£17,834
ICER with ERG correction			**£17,681**

It should be noted that the ICER presented does not reflect any other changes to the economic model besides widening the time horizon in the analysis. Changes to the utility values used in the model are discussed in the next section.

3.0 Use of utilities in the cost-effectiveness model

Summary of previous submission and Committee's comment

In response to the first Appraisal Committee request for analysis, the utilities used in the Addendum to the submission were based on quality-of-life data collected from RFHE3001 rather than derived from the general public.

Quality of life (QoL) data was collected in RFHE3001 using the Chronic Liver Disease Questionnaire (CLDQ) and SF-36. Norgine used a validated algorithm developed by Gray et al (2006) for mapping the SF-36 observations collected in RFHE3001 to EQ-5D utility values, however, further analysis was undertaken to establish the relationship between the observed overall CLDQ score and estimated EQ-5D index utility generated from the mapping exercise. [redacted] modelling was used to quantify the relationship between overall CLDQ and estimated EQ-5D index utility: each additional unit of the CLDQ score was found to confer an incremental utility of [redacted]

Additionally, Norgine applied a utility increment related to rifaximin treatment in the covert health state. This increment was taken from the figure published in Sanyal et al (2011), which reported CLDQ data from a post-hoc analysis of RFHE3001, showing the difference in least square means of time-weighted average values between overall CLDQ scores reported by subjects receiving either rifaximin or placebo. Only data from Canadian and USA patients enrolled in RFHE3001 were used for this QoL analysis since there was no validated Russian translation of the CLDQ available.

The Committee was unsure why the manufacturer had not presented results based on mapping SF-36 data collected from RFHE3001 directly to EQ-5D. The Committee considered that incorporating further modelling steps after the mapping exercise to quantify the relationship with CLDQ scores unnecessarily introduced further uncertainties in the analysis (ACD, section 4.8).

The Committee was concerned that the manufacturer used utilities estimated from the QoL study by Sanyal et al. (2011), which reported CLDQ data from a post-hoc analysis of RFHE3001. It noted that the study included QoL data for North American and Canadian patients only (219 of 299 patients) from RFHE3001 and that Russian patients were excluded from the analysis because there was no validated Russian translation of CLDQ, resulting in loss of data (ACD, section 4.8).

The Committee considered that although a utility benefit with rifaximin was very plausible, a utility benefit of 0.106 in the remission state was likely to be an overestimation. In addition, the Committee considered that the utility difference between the remission and the overt state was likely to be underestimated (ACD, section 4.9).

Given the concerns around methodology and the inconsistencies identified in the results available, the Committee considered that the utility estimates driving the model were not robust (ACD, section 4.9).

The Committee recommended that NICE requested further analysis, more specifically estimates of utilities from SF-36 QoL data collected from the RFHE3001 trial and mapped directly to the EQ-5D, using all observations in each relevant health state and adjusted for baseline utility (ACD, section 4.9).

Overview of method applied in the revised analysis

In response to the Committee requests, Norgine have undertaken scenario analysis where they have mapped SF-36 data from RFHE3001 to EQ-5D utility scores.

Norgine have analysed SF-36 patient data and presented their analysis both for the unadjusted and the adjusted data for baseline utility. We describe these in turn.

Unadjusted utilities

Norgine used the SF-12 subset of observed SF-36 QoL responses collected during RFHE3001 trial to calculate EQ-5D utility scores. This was done using the response mapping method developed by Gray et al (2006). Multiple imputation (SPSS 20, IBM Corp, Chicago) was used to impute missing responses to the SF-12.

As per the clinical study report (CSR), patients could undertake the SF-36 questionnaire (optional) on the following time points:

- Baseline assessment (visit 2)
- Days 28, 56, 84, 112, and 140
- End of study (EoS), which was at 168 ± 2 days (visit 15).

Norgine state that at baseline, EQ-5D utility was calculable for 139 placebo patients and 125 rifaximin patients, while at the end of month 6 data were available for 58 placebo patients (42%) and 78 rifaximin patients (62%).

Utility between the treatment arms of RFHE3001 trial for patients in the covert and in the overt states was compared with student's t-test statistical analysis.

Baseline adjusted utilities

To estimate adjusted utility values, Norgine excluded from the analysis patients for whom utility baseline values were missing. Only those EQ-5D values recorded during the covert state (i.e. prior to any HE episode) were included. Norgine estimated the change in EQ-5D from baseline for each discrete time point.

Missing values were inputted using linear interpolation between the two nearest neighbouring observed values. Graphical analysis was said to be conducted in Microsoft Excel.

Critique of the method applied in the revised analysis

Following the Committee's recommendations, Norgine took QoL data collected from RFHE3001 and used the mapped utilities from SF-36 to EQ-5D in the economic model, excluding any other intermediate modelling steps.

The ERG are generally satisfied with the methodology undertaken to analyse unadjusted utility data. However we have some concerns with regards to the adjusted utility data analysis. These are described below.

Unadjusted utilities - results

Norgine analysed the unadjusted utility data for the statistical difference between the placebo and the rifaximin arms of the model. The results were presented for all patients (***[redacted]1) and also for patients in the covert state (i.e. patients who experienced an HE episode were removed from the analysis). The latter is presented in ***[redacted]2.

[redacted]1

[redacted]

Norgine response to NICE request, page 8.

[redacted]2

[redacted]

Norgine response to NICE request, page 8.

Three issues concerning ***[redacted]1 and ***[redacted]2 should be discussed:

- Norgine report that there were no statistically significant differences in the unadjusted utilities between rifaximin and placebo at any time point. However none of the graphs report p-values for the estimated differences in utilities, so it is impossible to verify this statement.
- The difference between ***[redacted]1 and ***[redacted]2 is that only covert patients where considered in ***[redacted]2. The effect of removing patients who experienced a HE episode during RFHE3001 from the analysis is quite noticeable, especially after month 5. When these patients were excluded, the utility experienced by the remaining (covert) patients in both arms of the model is significantly higher. This suggests that patients who do not suffer a HE event experience a fairly stable utility in the covert state and across treatment arms.
- QoL for patients in both treatment arms seems to increase from baseline to month 1. While this scenario is easily understandable for rifaximin patients, it seems less obvious why this would be the case for placebo patients. Nonetheless it is likely that the increase in utility observed in the graphs is not statically significant.

Norgine undertook further statistical analysis where they have estimated:

1. The difference in utilities at the EoS between overt and covert patients (regardless of treatment allocation) (Table 2).
2. The difference in utilities at study baseline between overt and covert patients (regardless of treatment allocation) (Table 3).
3. The difference in utilities between baseline and EoS for patients who remained in the covert state (regardless of treatment allocation) (Table 4).
4. The difference in utilities between baseline and EoS for patients who experienced a HE episode (regardless of treatment allocation) (Table 5).

The analysis presented in Table 2 suggests that there is a statically significant difference in the utilities experienced at EoS between overt and covert patients. This was expected as patients experiencing a HE episode are likely to suffer a decrease in their QoL compared with patients who do not experience a breakthrough HE event. There is an expected loss of 0.168 (p-value = 0.000) in the utility experienced by a patient who suffered a HE episode, compared to a patient who remained in the covert state.

The analysis presented in Table 3 suggests that there is a statically significant difference in the utilities experienced at baseline between overt and covert patients. This was part of a subgroup analysis where for those patients experiencing (or not) a HE event, the difference in baseline utilities was assessed. At baseline, patients who then later on suffered a HE event, experience a decrement in their utility of 0.076 (p-value = 0.013). This suggests that patients who experience a HE event are worse off at baseline, and therefore might be sicker than patients who do not experience a HE event at baseline. This can potentially reveal a bias in the baseline population.

Table 4 presents the paired samples comparison of baseline and EoS utility for patients who remained in the covert state (i.e. who did not experience a HE event during RFHE3001). There was no statistically significant difference between baseline and EoS EQ-5D mean scores observed for these patients. This is regardless of treatment allocation and represents a reasonable scenario, where patients who do not experience a HE episode experience stable QoL over time. This also suggests

that the difference from baseline to EoS in EQ-5D values shown in ***[redacted]1 is likely to be statistically insignificant.

Finally, Table 5 presents the paired samples comparison of baseline and EoS utility for patients who experienced a HE event during RFHE3001. There was no statistically significant difference between baseline and EoS EQ-5D mean scores observed for these patients. This is regardless of treatment allocation. The interpretation of this result is less obvious as it would be expected that the QoL of these patients deteriorates over time. Taking into account that there is a statistically significant difference in the utility experienced between patients in the covert and the overt states at the EoS, this result could potentially be explained by the hypothesis that patients experiencing a HE episode already have lower EQ-5D scores at baseline (so they experience a lower QoL from the beginning of the study, which is in fact suggested by the analysis presented in Table 3).

Table 2. Utilities at EoS in the covert and overt states.

Group Statistics

	BRKHE	N	Mean	Std. Deviation	Std. Error Mean
Month 6 / EoS EQ-5D	NO	150	.63089	.234848	.019175
	YES	59	.46312	.257722	.033553

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Month 6 / EoS EQ-5D	Equal variances assumed	2.385	.124	4.521	207	.000	.167768	.037109	.094609	.240927
	Equal variances not assumed			4.341	98.004	.000	.167768	.038645	.091078	.244458

Table 3. Comparison of baseline utility for subjects who did vs. those that did not have an episode of breakthrough HE.

Group Statistics

	BRKHE	N	Mean	Std. Deviation	Std. Error Mean
Baseline EQ-5D	NO	168	.59593	.232598	.017945
	YES	96	.52026	.243064	.024808

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Baseline EQ-5D	Equal variances assumed	.640	.424	2.501	262	.013	.075668	.030251	.016101	.135235
	Equal variances not assumed			2.471	190.727	.014	.075668	.030618	.015275	.136061

Table 4. Paired samples comparison of baseline & Month 6 / EoS utility for subjects who remained in covert state.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Baseline EQ-5D	.61592	139	.223112	.018924
	Month 6 / EoS EQ-5D	.62365	139	.239076	.020278

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	Baseline EQ-5D - Month 6 / EoS EQ-5D	-.007734	.198845	.016866	-.041083	.025615	-.459	138	.647

Table 5. Paired samples comparison of baseline & EoS utility for subjects who had a breakthrough HE episode

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Baseline EQ-5D	.50204	54	.235016	.031982
	Month 6 / EoS EQ-5D	.43889	54	.254338	.034611

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	Baseline EQ-5D - Month 6 / EoS EQ-5D	.063148	.242358	.032981	-.003003	.129299	1.915	53	.061

Adjusted utilities – results

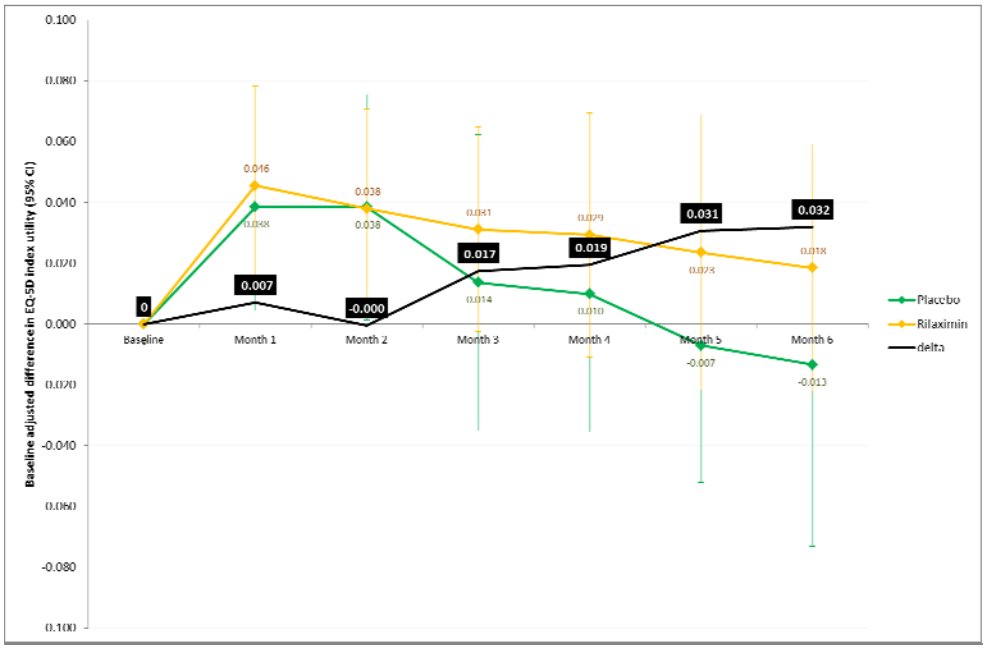
Norgine also analysed the utility data adjusted for baseline utility. However the only output of the analysis was Figure 3 presented below.

Norgine conclude that by month 6 there is an incremental difference of 0.032 favouring rifaximin patients. This is used in the economic analysis as the incremental utility attributable to rifaximin (when compared to placebo) in the covert state. Hence this utility gain is not related to avoiding HE episodes.

The ERG have several concerns with the adjusted analysis:

- The Committee requested that the adjusted analysis was undertaken, however Norgine do not provide much detail on this analysis. Furthermore the adjusted estimate of 0.032 is used in the economic analysis hence it is quite surprising that the unadjusted analysis was reported with great level of detail while the adjusted analysis was barely reported.
- Figure 3 does not provide p-values. This means that it is impossible to assess if the differences in utility reported (including the 0.032 value) are statistically significant.
- Figure 3 reports the difference in EQ-5D utility at different points in time between rifaximin and placebo patients, with no differentiation between patients in the covert and in the overt state. As seen before in ***[redacted]1 and ***[redacted]2, excluding patients who experienced a HE event could potentially have a great impact on this analysis. As previously mentioned, removing patients who experienced a HE event could potentially flatten the curves as patients in the covert state tend to have a fairly stable QoL throughout the analysis. This also means that the difference in utility of 0.032 at the EoS could be attributable to HE episodes.
- The face validity of Figure 3 is somewhat questionable:
    - The EQ-5D utility scores appear to be rather low both for the rifaximin and the placebo arm (range: -0.013 to 0.046), especially when compared with the utility values from the unadjusted analysis (range: [redacted]).
    - The effect of the adjustment is surprisingly large, particularly in the absence of details about how the adjustment was done.

Figure 3. Baseline-adjusted difference in EQ-5D utility at each time point



Norgine response to NICE request, page 10.

Utility values used in the economic analysis

Table 6 presents the mean health state utility values used in the revised cost-effectiveness analysis. One of the key observations that can be drawn from this approach is that the utility value associated with the overt health state of the rifaximin arm is now higher than the one associated with the overt health state of the placebo arm. In other words, the values now used imply that rifaximin offers a considerable QoL gain to patients in the overt state (and not just through prolonged time to HE events). This contrasts with the original model submitted by Norgine, in which QoL gains were linked to the difference in utilities between the covert and overt states and (subsequently on the addendum) to the use of rifaximin in the covert state.

The ERG have some concerns regarding the three base utility values used in the analysis (note that the remainder values are obtained through calculation). These are now detailed.

Utility value associated with the covert state for patients on the placebo arm of the model

The estimated utility value is 0.568, however the ERG could not trace this value back to its original source. It is not clear in the manufacturer revised report if this value was obtained through the adjusted EQ-5D utility analysis or through any other source.

The difference in utility assumed between the covert and the overt states in the model

The estimated utility value is 0.286. This is the incremental utility associated with preventing a patient from experiencing a HE event (i.e. this represents the loss in QoL that a patient is expected to experience if he suffers a HE event).

The Committee were concerned that in their previous submission the manufacturer had underestimated the gain in utility associated with preventing a HE event. In that sense, the approach

followed in the revised analysis can be considered an improvement, as it led to a higher estimate (Table 6).

However, the estimate used comes from the manufacturer's original submission (and not their revised analysis), where utility values were taken from a study commissioned by Norgine and health state preferences were derived from the general public. Upon the original submission, the Committee was concerned that the utilities estimated from the general public may not be reliable and were too high for people with underlying liver disease and therefore recommended that Norgine used the SF-36 utility data collected in RFHE3001.

Additionally, the revised approach departs even further from the previous analysis as not only did Norgine go back to using values from the original submission, but they have decided to use different utility values than the ones employed in the original cost-effectiveness model. While in the original economic analysis Norgine believed that the time-trade-off (TTO) utility values were suited for the model, in their revised analysis they decided to use the standard gamble (SG) utility values, originally incorporated in their sensitivity analysis. To note is that the TTO incremental utility value is [redacted], so there is not a major difference from the SG incremental utility estimate of 0.286. Nonetheless, no rationale was provided for this decision.

More importantly, Norgine claim to have used the SG utility increment as there were no observations from the SF-36 scores in the overt state in RFHE3001. They then add that although observations in the overt state (n=67) were available from RFHE3001, the resulting value of 0.463 is most likely to be a significant over-estimate since it mainly represented patients with breakthrough HE with a Conn score of 1 plus a 1 grade increase in asterixis, and therefore did not represent the utility of patients in Conn scores 2, 3 or 4.

The ERG worry about the lack of coherence and transparency of these statements.

Firstly, it seems unreasonable that no utility observations were captured for patients in the overt state. Even though the ERG are not clear if HE patients were called back for visit 15 and had their utility recorded (as the CSR and the submission documents do not specify this), there seems to be data available for these patients.

Secondly, the unadjusted analysis of utilities reports analysis undertaken for patients in the overt state. Contradicting their first argument, Norgine claim that there were observations captured for patients experiencing a HE event but that the resulting value 0.463 is likely to be an overestimation. Again, the ERG cannot trace this value back and are unaware of the source of this estimate, as well as of the statistical analysis around it (for example p-values and the population baseline characteristics in terms of Conn scores).

The difference in utility assumed between rifaximin and placebo

The estimated utility value is 0.032, regardless of the heath state the patient is in. This is the incremental utility associated with the patient being on rifaximin (i.e. this represents the gain in QoL that a patient is expected to experience if he is on rifaximin treatment, regardless of the fact that he might experience a HE event or not).

The Committee were concerned that in their previous submission the manufacturer had overestimated the gain in utility associated with rifaximin treatment. In that sense, the approach

followed in the revised analysis can be considered an improvement, as it led to a lower estimate (Table 6).

However, the ERG are concerned with the lack of details provided by the manufacturer as to how this estimate was obtained. As previously mentioned, this value was presented in Figure 3 but no statistics were provided. Therefore we cannot know the sample size, the statistical significance and other crucial statistics to assess the validity of this approach. Furthermore, the ERG have raised some issues with regards to the face validity of Figure 3 (previous subsection of the report).

Finally, it should be noted that the incremental gain in QoL associated with rifaximin treatment is now also assumed for the overt state. This means that patients experiencing a HE event who are on rifaximin are expected to have a higher utility during the event period than patients experiencing the event who are on placebo. The clinical plausibility of this scenario should be considered by the Committee.

Table 6. Mean utilities used in models by health states

Health state		Original utilities	Revised utilities	Source
Covert	Rifaximin	[redacted]	0.600	Calculation: 0.568 + 0.032
	Placebo	[redacted]	0.568	?
Overt	Rifaximin	[redacted]	0.314	Calculation: 0.600 - 0.286
	Placebo	[redacted]	0.282	Calculation: 0.568 - 0.286
Difference (Covert minus Overt)	Rifaximin	[redacted]	0.286	Study used in the original submission (SG estimates)
	Placebo	[redacted]	0.286	Study used in the original submission (SG estimates)
Difference (rifaximin minus placebo)	Covert	[redacted]	0.032	Adjusted utility analysis from SF-36 data in RFHE3001
	Overt	[redacted]	0.032	Adjusted utility analysis from SF-36 data in RFHE3001

Implications

After incorporating the revised utility analysis in the model, Norgine reported an ICER of £29,076. However the ERG found a small mistake in the economic model related with the age weights applied to the utility calculations and we have corrected this. Table 7 shows that using the revised utility analysis in the economic model leads to an ICER of £28,805 after the ERG correction.

Table 7. ICER with revised utilities (with ERG correction)

Cost-effectiveness results per patient over lifetime	Rifaximin (1)	Placebo (2)	Incremental value (1-2)
Total costs £	£28,874	£6,925	£21,949

Cost-effectiveness results per patient over lifetime	Rifaximin (1)	Placebo (2)	Incremental value (1-2)
QALYs	3.850	3.088	1.241
ICER			**£28,805**

The assumption that patients on rifaximin benefit from QoL gain just by being on rifaximin treatment (i.e. not by avoiding the occurrence of HE episodes) was thoroughly discussed in the previous Committee meeting. Since in the revised analysis the manufacturer kept this assumption, not only for the covert but also for the overt state, the ERG undertook some exploratory analysis to assess the impact of removing the incremental utility gain associated with rifaximin vs placebo (Table 8) and report the results of the analysis in Table 9.

The third column in
Table 9 presents the final ICER when no incremental utility is considered between the rifaximin and the placebo arms for the covert state (scenario 1), with the incremental utility gain in the overt state assumption in place.

The fourth column presents the ICER when no incremental utility is considered between the rifaximin and the placebo arms for the overt state (scenario 2), with the incremental utility gain in the covert state assumption in place.

Finally the last column presents the ICERs when no incremental utility gain between the rifaximin and the placebo arms for both heath states (overt and covert) is considered. When the same utility values are applied (scenario 3: QoL gains are only accrued through reduced recurrence of HE episodes and not through treatment itself) the lifetime ICER increases from £28,805 to £39,296

Removing the incremental utility gain between rifaximin and placebo in the covert state has the highest impact on the final ICER driving the base case value up by £10,379. To note is that the incremental utility gain is considerably low (0.032). Importantly, the unadjusted analysis of SF-36 derived utilities found no statically significant difference between rifaximin and placebo for patients in the covert state. Unfortunately, Norgine do not present the equivalent analysis with respective p-values for the adjusted data. Therefore, the ERG are concerned with the use of this value in the model given its significant impact on the final ICER.

Table 8. Utility values used in ERG exploratory analysis

Scenario 1 (S1)		Norgine revised model	ERG exploratory analysis
Covert	Rifaximin	0.600	0.568
	Placebo	0.568	0.568
Overt	Rifaximin	0.314	0.314
	Placebo	0.282	0.282
Scenario 2 (S2)		**Norgine revised model**	**ERG exploratory analysis**
Covert	Rifaximin	0.600	0.600
	Placebo	0.568	0.568

Overt	Rifaximin	0.314	0.282
	Placebo	0.282	0.282
Scenario 3 (S3)		**Norgine revised model**	**ERG exploratory analysis**
Covert	Rifaximin	0.600	0.568
	Placebo	0.568	0.568
Overt	Rifaximin	0.314	0.282
	Placebo	0.282	0.282

Table 9. Impact of the utility increment on the ICER (with ERG corrections)

Time perspective	Revised analysis with new utilities	Revised analysis with new utilities (no increment between arms in the covert state) (S1)	Revised analysis with new utilities (no increment between arms in the overt state) (S2)	Revised analysis with new utilities (no increment between arms in the covert and overt states) (S3)
Lifetime ICER	**£28,805**	**£39,184**	**£28,866**	**£39,296**

Even though Norgine present the revised analysis with the updated utility values derived from SF-36 data in RFHE3001 they still claim that these utility data are not the most appropriate to use in the economic analysis, and therefore suggest that CLDQ data from Sanyal et al (2011) are used instead, which would result in a 0.106 utility gain for patients treated with rifaximin compared with patients treated with placebo.

Norgine also state their preference for the method used previously (whereby they use the mapped SF-36 to EQ-5D utility values to establish the relationship with CLDQ measures). This is justified through the following arguments:

- Domains of SF-36 have wider variance than CLDQ domains, suggesting that the former is a less precise instrument for measuring QoL in patients with underlying neurocognitive impairment.
- CLDQ is a disease specific QoL measure (as opposed to SF-36).
- The assessment of patients' QoL with SF-36 was optional, while the assessment with CLDQ was mandatory hence the likelihood of non-random missing data in the SF-36 dataset is higher than in the CLDQ dataset.
- HE patients are unlikely to be able to respond adequately to a survey and the 30-day recall period for the SF-36 questions could be contaminated by subclinical deterioration in those patients who experienced a HE episode.

However the following arguments should also be considered:

- There was no significant difference in the CLDQ fatigue domain scores between rifaximin and placebo in RFHE3001, whereas the Sanyal et al (2011) post-hoc analysis reported statistically significant improvement with rifaximin across all items in the fatigue domain. In

particular, the Committee noted that the post-hoc analysis indicated that there were significant differences in the drowsiness and sleepiness score of the CLDQ fatigue domain, whereas the specific Epworth Sleepiness Scale used in the trial indicated no consistent differences between the placebo and rifaximin groups in change from baseline.

- Sanyal et al. (2011), which reported CLDQ data from a post-hoc analysis of RFHE3001, included QoL data for North American and Canadian patients only (219 of 299 patients) and Russian patients were excluded from the analysis because there was no validated Russian translation of CLDQ, resulting in loss of data.

- Arguably, if HE patients are unlikely to be able to respond adequately to a survey this would also affect their capability of responding to the CLDQ questionnaire, even if this is a liver-specific QoL measure. Furthermore, the CLDQ assessments took place on the same days of the (optional) SF-36 completion, therefore if Norgine believe that the 30-day recall period for SF-36 questions could be contaminated by subclinical deterioration in those patients who had experienced a HE episode, it seems that the same argument would apply to CLDQ responses.

- Finally, Norgine claim that a time weighted methodology appears more appropriate but the area under the curve approach could also be taken with SF-36 data.

4.0 Mortality

Summary of previous submission and Committee's comment

Norgine used RFHE3002 data (including all patients) to model mortality in four health states of the Markov structure, respectively:

- Time to death from the initial covert state
- Probability of mortality within 30 days of the first observed HE episode
- Time to death from the subsequent covert state
- Probability of mortality within 30 days of any subsequent HE episode.

Data from RFHE3002 was extrapolated over 5 years to model time to death form the initial and subsequent covert states. While a log-normal distribution was used to model time to death from the initial covert state, a Weibull distribution was used to model time to death from the covert state after any subsequent HE event.

Mortality associated with the overt states was not modelled using survival analysis. The probability of death in the first overt state was calculated as the number of deaths within 30 days of onset of the first observed HE event ([redacted]). Subsequent overt mortality was calculated as the proportion of subjects who entered any subsequent overt state who died within 30 days ([redacted]).

However, the Committee was concerned that the model predicted a difference of 3.6% in the risk of mortality with rifaximin compared with placebo during the first 6 months of the model and a difference of up to 8% over the 5-year time horizon (ACD, section 4.11).

The Committee considered whether it was clinically plausible to expect a differential mortality benefit with rifaximin plus lactulose compared with lactulose only. It noted that the manufacturer's updated analysis demonstrated that the time to subsequent overt HE episodes decreased as the number of episodes increased. The Committee expressed concern that the model predicted an increasing differential mortality benefit for rifaximin when clinical experience indicates decreasing clinical efficacy over time in preventing overt HE episodes (ACD, section 4.12).

The Committee recommended that further analyses be requested excluding mortality benefit in the remission state and incorporating a clinically plausible diminishing mortality benefit over time (ACD, section 4.12).

Overview of method applied in the revised analysis

Norgine sought additional clarification from NICE's Technical Team on how to address the Committee's request in a clinically plausible manner. Norgine concluded that if the lifetime horizon perspective was adopted (as per the Committee suggestion), the issue of increasing mortality benefit over time in the economic model would be solved. Widening the time horizon of the economic analysis lead to a more clinically plausible diminishing mortality benefit with rifaximin compared with placebo (base case in ***[redacted]4)

Norgine explain that the mortality rate in the initial covert state (i.e. before experiencing a HE event) and in the subsequent covert state (i.e. after the patient experienced a HE event) are not expected to be similar from a clinical point of view. Based on the analysis undertaken by Bustamante et al, 1999

Norgine claim that the hazard of death is highest within the first three months following a HE event. As the model assumes that patients enter the subsequent covert state 30 days after they experience a HE event, these patients are arguably more likely to die than those sitting in the initial covert state (i.e. before experiencing a HE event).

Norgine add that it would not be clinically plausible to assume that 30 days after a HE event patients would automatically return to their initial baseline death hazard.

[redacted]4

[redacted]

Norgine response to NICE request, page 15.

As per the Committee request, Norgine have also undertaken scenario analysis to assess the impact of removing the mortality benefit of rifaximin compared to placebo in the covert and the overt states of the model, respectively. Three scenarios were considered:

1. Mortality rate in the initial covert state is equal to the mortality rate in the subsequent covert health state.

   In this scenario it was assumed that patients in the subsequent covert state (i.e. patients who have experienced a HE event and then return to the covert state 30 days after the episode) experience the same mortality rates as patients in the initial covert state (i.e. patients who have not experienced a HE event). This is represented by the Scenario 2 curve in ***[redacted]4.

2. Mortality in the overt state equals mortality in the covert state.

   In this scenario it was assumed that patients in the overt state experience the same mortality rates as patients in the covert state. This assumption implies that there is no increase in mortality while patients experience a HE episode. This is represented by the Scenario 3 curve in ***[redacted]4.

3. Scenario 1 and 2 combined – there are no mortality benefits associated with rifaximin treatment.

Scenario 1 and scenario 2 were combined to reflect a situation where rifaximin would not have any impact on the mortality of HE patients. This is represented by the Scenario 4 curve in ***[redacted]4.

Critique of the method applied in the revised analysis

Norgine did not change the methodology previously used to estimate mortality within the economic model. Widening the time perspective of the analysis revealed that [redacted] (***[redacted]4).

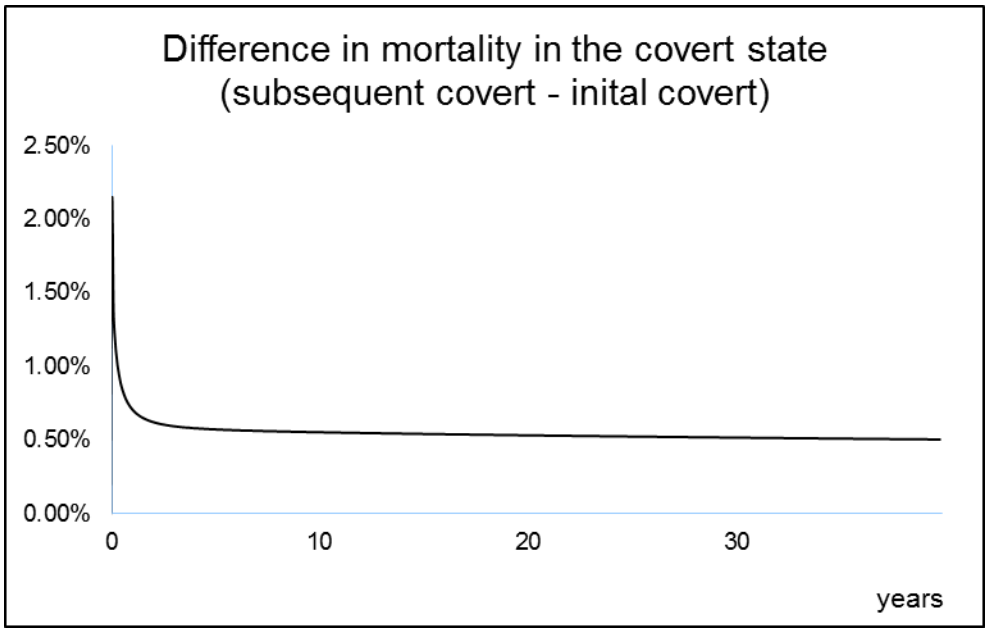
The ERG are generally satisfied with the approach taken. Furthermore Norgine undertook scenario analyses to explore the impact of mortality in the final ICERs (explored in the next subsection).

It seems reasonable and clinically plausible that rifaximin impacts mortality rates experienced by HE patients. However the clinical plausibility of using different mortality rates in the four health states of the model should be considered. More specifically, three clinical aspects should be discussed:

The difference in mortality between initial covert and subsequent covert states

Norgine claim that mortality in the subsequent covert state is supposedly higher for the initial 3 months after the HE event (Bustamante et al, 1999). It seems reasonable that after an HE event patients do not immediately return to the baseline mortality risk they experienced before the HE event. However in the economic model the risk of death in the subsequent covert state is always higher than the mortality risk in the initial covert state. Despite this, the difference in mortality is relatively small, especially after year 5, where the difference is around 0.5%, and remaining stable until year 40. Figure 5 presents the difference in mortality between initial and subsequent covert states throughout time.

Figure 5. Difference in mortality in the covert state



The difference in mortality between covert and overt states

The ERG find plausibility in the argument that patients experience a higher mortality risk while suffering from a HE event.

The difference in mortality between initial overt and subsequent overt states

Mortality associated with the overt states was not modelled using survival analysis. The probability of death in the first overt state was calculated as the number of deaths within 30 days of onset of the first observed HE event (□). Subsequent overt mortality was calculated as the proportion of subjects who entered any subsequent overt state who died within 30 days (□).

The ERG believe that the clinical plausibility of experiencing a lower mortality risk in the subsequent overt state compared with the initial overt state should be considered, as it would seem more plausible to have an increasing mortality risk with the increased frequency of HE events.

Implications

Mortality rates

Table 10 allows comparison across observed mortality in RFHE3001 and RFHE3002, mortality rates for HE patients using CPRD data, and the mortality estimates generated by the revised model. The latter show that at 6 months around 10% of patients on placebo are estimated to be dead, whilst for patients on rifaximin the estimated death rate is 7%. The corresponding values from RFHE3001 show that while the mortality in the rifaximin arm was similar to the modelled one, the economic model tends to overestimate mortality on placebo patients. However, mortality data from RFHE3001 was considered not to be mature enough to draw any economic conclusions.

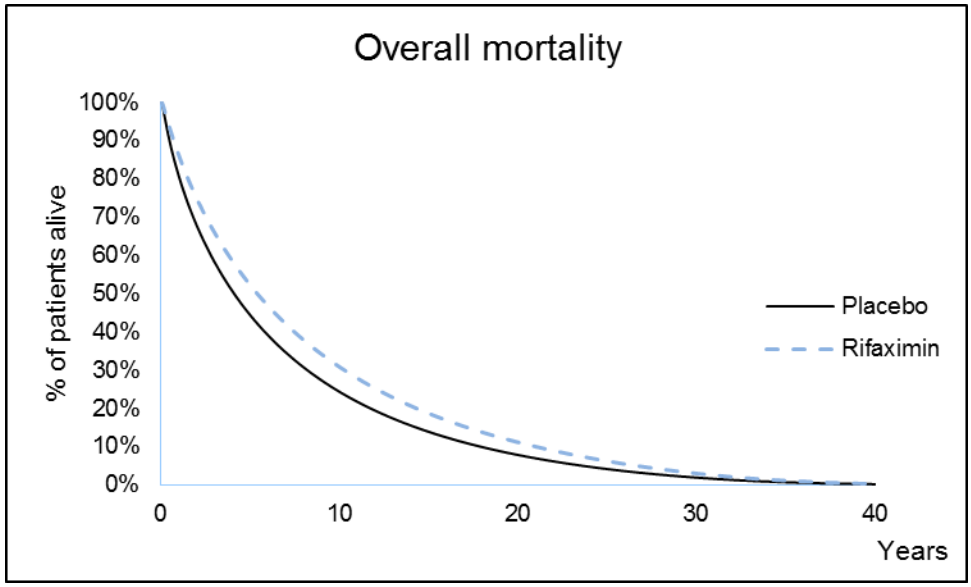
The 2-year mortality rate for rifaximin patients from the revised economic model is [redacted]. For patients on lactulose this comparison is not possible as RFH3002 was a single arm study.

The 5-year mortality rates are around 48% in the rifaximin arm and 56% in the placebo arm. This means that at 5 years, rifaximin plus lactulose have an incremental effect of 8% in terms of deaths avoided, when compared with lactulose alone. Our clinical expert indicated that while the incremental effect seems reasonable, the overall death rates seem low for patients in both arms for all points in time (especially at 5 years). The clinical expert added that a higher number of liver transplants would be expected amongst HE patients (only 1 liver transplant was observed on the placebo arm of RFHE3001). At 40 years, mortality rates in the rifaximin and placebo arms of the model are identical, 100% having died (Figure 6).

Table 10. Mortality rates from different sources

Mortality	1 mnth	6 mnths	1 year	2 years	3 years	4 years	5 years	Lifetime (40 years)
RFHE3001								
Rifaximin	-	7.14%	-	-	-	-	-	-
Placebo	-	6.92%	-	-	-	-	-	-
RFHE3002								
Overall	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
Continuing RFX from 3001	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
New patients	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-
CPRD 6 mnth survivors	3.1%	14.2%	19.7%	32.8%	38.3%	43.7%	47.4%	-
Revised model								
Rifaximin	0.29%	6.69%	13.69%	24.98%	33.95%	41.39%	47.71%	99.77%
Lactulose	0.29%	10.30%	19.15%	32.07%	41.66%	49.30%	55.59%	99.82%

Figure 6.Overall mortality in the model



ICERs

As per Norgine scenario analysis, Table 11 shows the impact of mortality on the final revised ICER. It should be noted that the base case ICER presented on the second column does not include the utility adjustments presented on Section 4. Furthermore, the ERG found a small mistake in the model. After correcting this, the final lifetime ICER came down to £17,681.

The third column on Table 11 presents the impact on the final ICER of assuming the same mortality in the subsequent covert state and in the initial covert state, therefore assuming that there is no increase in mortality risk 30 days after a HE episode. This has a considerable impact, increasing the final ICER to £21,773. To note is that the difference in mortality risk between the covert and overt states is assumed in this scenario.

The fourth column on Table 11 shows the impact on the final ICER of assuming the same mortality risk in the overt and the covert states of the model, therefore assuming that there is no increase in mortality risk while the patient experiences a HE event (compared to when the patient is on the covert state). This has a small impact, increasing the final ICER to £21,606. To note is that the difference in mortality risk between initial and subsequent HE events both for the covert and overt states is assumed in this scenario.

Finally, when we assume that HE events do not have any kind of impact on mortality, the final ICER goes from £17,681 to £31,632. This scenario assumes that there no difference in mortality between covert and overt health states, as well as no difference in the mortality risk between initial and subsequent health states (i.e. this combines the previously described scenarios).

Table 11. Impact of mortality decomposed (with ERG corrections)

Lifetime	Base case	Same mortality assumed for the initial and subsequent covert states (1)	Same mortality assumed for the covert and the overt states (2)	Mortality not affected by breakthrough overt episodes (1+2)
ICER	**£17,681***	£21,773	£21,606	£31,632

*This value does not include the utility adjustments

5.0 Economic modelling results

Base case

Norgine presented a revised cost-effectiveness analysis of rifaximin-α 550 mg for the prevention of recurrence of HE in patients with liver cirrhosis and reported an ICER of £17,834 over lifetime. However the ERG found a small mistake in the age weights applied to the utility values in the model. After correcting this, the final ICER decreased to £17,681 (Table 12).

Table 12. Cost-effectiveness results in the revised analysis

Cost-effectiveness results per patient over lifetime	Rifaximin (1)	Placebo (2)	Incremental value (1-2)
Total costs £	£28,874	£6,925	£21,949
QALYs	4.452	3.211	1.241
ICER			£17,834
ICER with ERG correction			**£17,681**

As explained in Section 4, it is the manufacturer opinion that the revised utility values should not be used in the base case analysis. Therefore, using the lifetime perspective but keeping the utility values used in the previous submission (CLDQ values from Sanyal et al 2011) generated an ICER of £17,681 with the ERG correction.

Since the Committee requested that the revised utility data were included in the base case analysis, the ERG combined the revised analysis undertaken by Norgine and present the final ICER in Table 13. After the ERG correction (mentioned previously), the final base case ICER is **£28,805** per QALY.

Table 13. ERG cost-effectiveness results in the revised analysis (all changes considered)

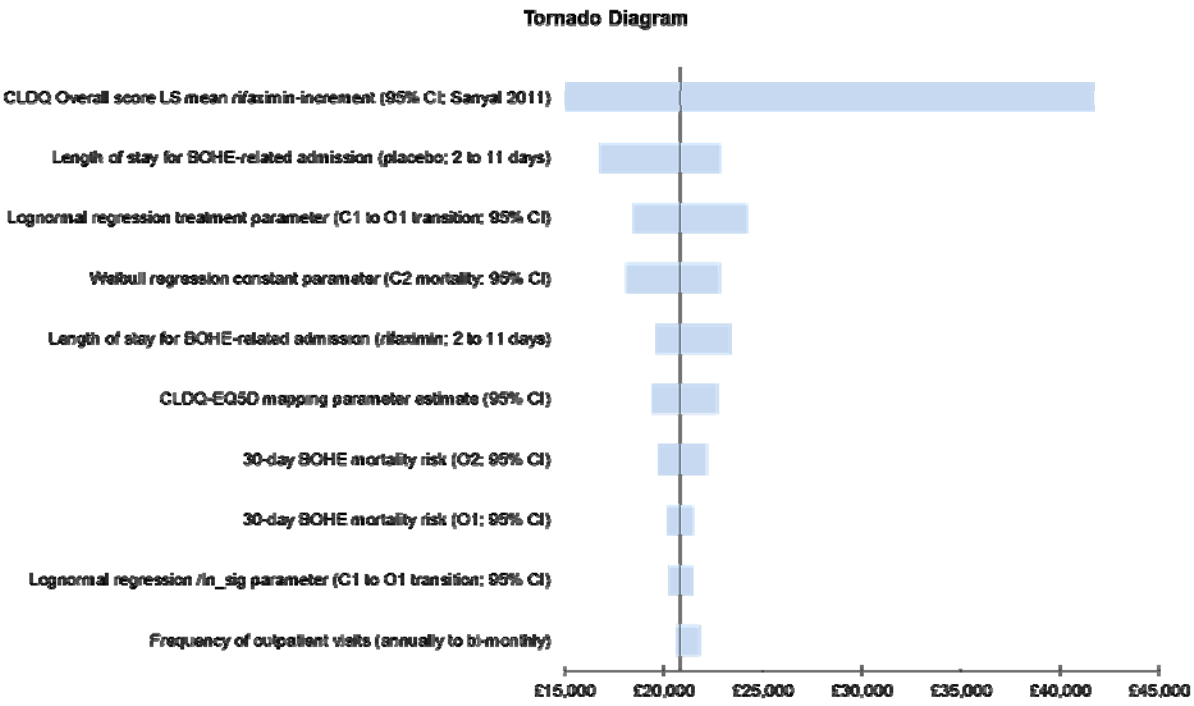
Cost-effectiveness results per patient over lifetime		Rifaximin (1)	Placebo (2)	Incremental value (1-2)
Lifetime horizon perspective (old utility values)	Total costs £	£28,874	£6,925	£21,949
	QALYs	4.452	3.211	1.241
	ICER			£17,681
Lifetime horizon perspective and revised utility analysis	Total costs £	£28,874	£6,925	£21,949
	QALYs	3.850	3.088	0.7620
	ICER			**£28,805**

Sensitivity analysis

Norgine undertook one-way and probabilistic sensitivity analysis.

The output of the one-way sensitivity analysis is presented in Figure 7. This analysis was performed for the 5-year base case ICER including the CLDQ utility values. The ERG do not see much value in the analysis presented as it basically reports the impact of varying the parameters included in Celgene's previous analysis and does not include the revised model parameters and assumptions included in the updated submission (lifetime time horizon and SF-36 derived utilities).

Figure 7. One-way sensitivity analysis

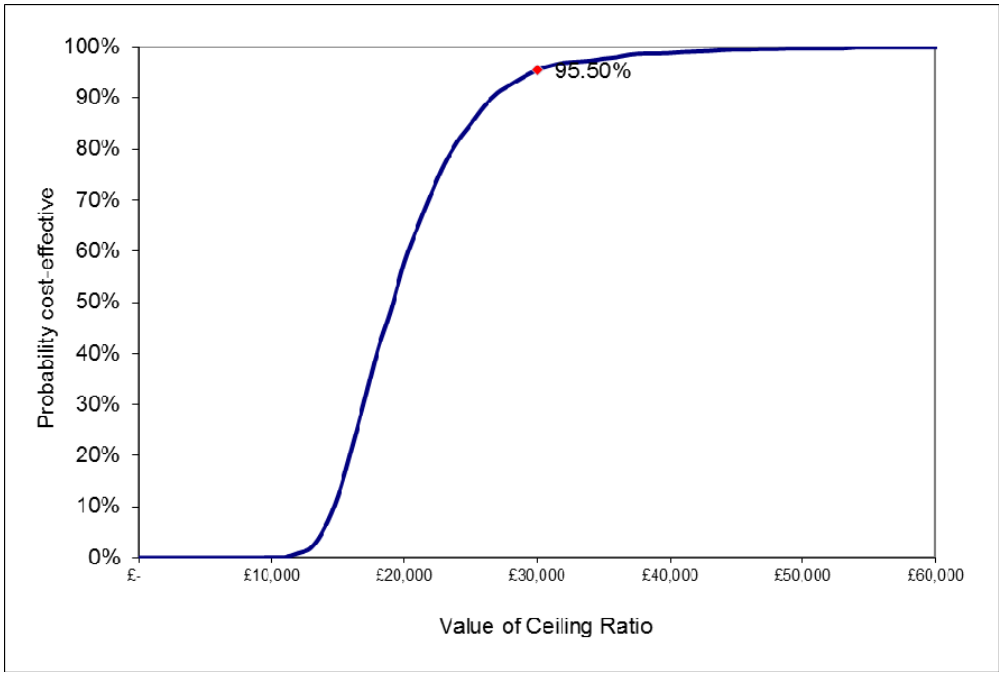


Probabilistic sensitivity analysis (PSA) was undertaken for different scenarios and was based on 10,000 simulations. Model parameters were varied according to different probability distributions, which were reported in Table 6 of the manufacturer revised submission (p 28). The scenarios considered for the PSA are described below, together with some of the reported cost-effectiveness acceptability curves (CEACs).

Lifetime horizon (CLDQ utilities)

Norgine undertook PSA to assess the impact of varying model parameters on the final lifetime (42 years) ICER. Figure 8 presents the CEAC. The probabilistic ICER was reported to be £18,144 and at a willingness to pay of £30,000 there was a 95.5% probability of rifaximin being cost-effective when compared with lactulose.

Figure 8. CEAC for Norgine base case analysis over lifetime

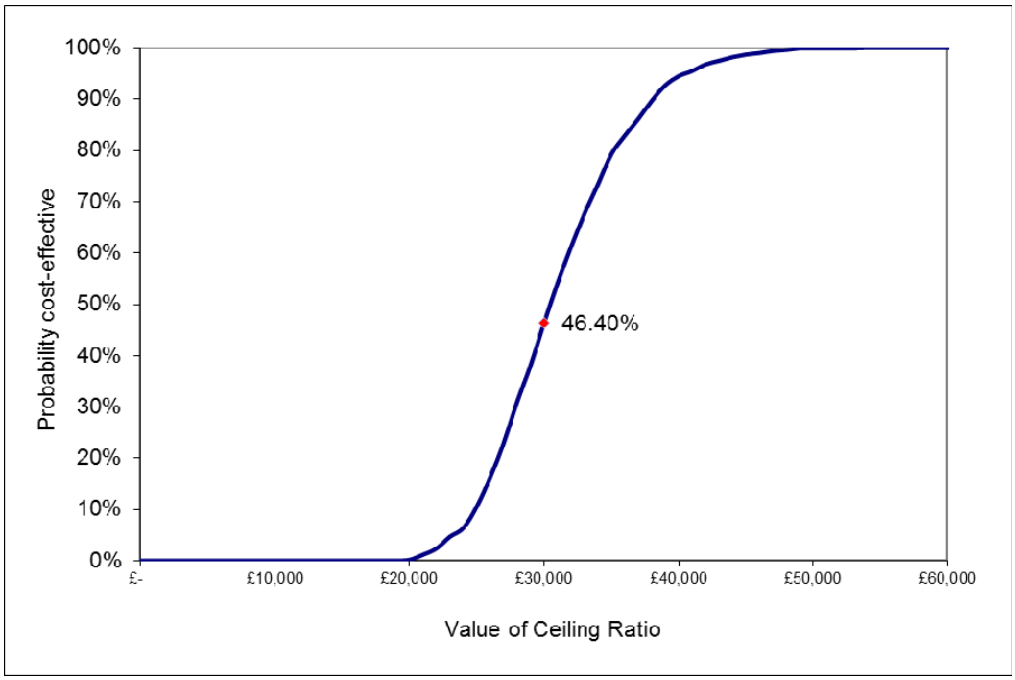


Norgine response to NICE request, page 23.

Lifetime horizon and SF-36 derived utilities

Norgine undertook PSA to assess the impact of varying model parameters on the final lifetime (42 years) ICER when SF-36 utility values were used in the economic model. Figure 9 presents the CEAC. The probabilistic ICER was reported to be £29,668 and at a willingness to pay of £30,000 there was a 46.4% probability of rifaximin being cost-effective when compared with lactulose.

Figure 9. CEAC when SF-36 derived utilities are used over lifetime



Norgine response to NICE request, page 23.

The ERG believe that this PSA scenario should be the one considered for the purpose of assessing the uncertainty within the economic model as this includes the SF-36 patient utility data and uses the lifetime time perspective.

Mortality scenario 1 (mortality rate is the initial covert state is equal the mortality rate in the subsequent covert health state) with lifetime horizon

Norgine undertook PSA to assess the impact of varying model parameters on the final lifetime ICER when the mortality rates in the initial and subsequent covert states were assumed to be the same in the economic model. The CEAC is presented in Figure 16 of the manufacturer submission. The probabilistic ICER was reported to be £22,324 and at a willingness to pay of £30,000 there was a 79.2% probability of rifaximin being cost-effective when compared with lactulose.

Mortality scenario 2 (mortality in the overt state equals mortality in the covert state) with lifetime horizon

Norgine undertook PSA to assess the impact of varying model parameters on the final lifetime ICER when the mortality rates in the covert and the overt states were assumed to be the same in the economic model. The CEAC is presented in Figure 17 of the manufacturer submission. The probabilistic ICER was reported to be £22,111 and at a willingness to pay of £30,000 there was a 80.6% probability of rifaximin being cost-effective when compared with lactulose.

Mortality scenario 1 and 2 combined (there are no mortality benefits associated with rifaximin treatment) with lifetime horizon

Norgine undertook PSA to assess the impact of varying model parameters on the final lifetime ICER when mortality benefits associated with rifaximin were excluded from the economic model. The CEAC is presented in Figure 18 of the manufacturer submission. The probabilistic ICER was reported to be £32,420 and at a willingness to pay of £30,000 there was a 37.1% probability of rifaximin being cost-effective when compared with lactulose.

As previously mentioned in Section 4, the scenario analysis around mortality are useful to the extent that they show the impact of modelled mortality in the final ICER. The same applies for the undertaken PSA of the different mortality scenarios. As noted in the previous ERG report, mortality still appears to have some impact on the final ICER however this is not concerning.

6.0 Conclusion

Having considered the addendum to the original submission undertook by Norgine, the Committee concluded that the ICER resulting from the analysis £20,799 was not plausible based on the uncertainties around model parameters and assumptions.

In this section of the report we summarise the uncertainties associated with the economic analysis reported on the addendum, we provide a brief recap of Norgine's approach to deal with these, and finally present the implications of the revised analysis.

Uncertainties in the previous analysis

The uncertainties in Norgine's previous analysis related to the following matters:

- A 5 year time horizon was used in the economic model. This was considered inappropriate for the purpose of capturing all the relevant costs and benefits associated with rifaximin. The Committee suggested that a lifetime time horizon was employed in the economic analysis.
- Norgine used SF-36 observations collected in RFHE3001 to map to EQ-5D utility values. However, further analysis was undertaken to establish the relationship between CLDQ scores and the estimated EQ-5D index utility generated from the mapping exercise. Introducing further modelling steps after the mapping exercise to quantify the relationship with CLDQ scores was considered unnecessary and deemed to introduce further uncertainties in the analysis. The Committee asked that additional analysis was undertaken employing mapped SF-36 observations directly to EQ-5D utility values, using all observations in each relevant health state and adjusting these for baseline utility.
- The submitted model predicted a difference of 3.6% in the risk of mortality with rifaximin compared with placebo during the first 6 months of the model and a difference of up to 8% over the 5-year time horizon. This was considered to be unreflective of clinical reality, where a diminishing benefit in mortality would be expected over time.
- The Committee requested that a full probabilistic sensitivity analysis was undertaken for the revised analysis.

Norgine's approach in the revised analysis

In their revised analysis Norgine have taken the following steps:

- A lifetime time horizon was used in the economic analysis.
- Scenario analysis was undertaken whereby the utilities used in the model were obtained by mapping SF-36 observations collected in RFHE3001 to EQ-5D utility values directly (unadjusted and adjusted utility analyses were reported). However the economic model also included utility values derived from other sources.
- Widening the time horizon of the economic analysis solved the problem of the increasing benefit in mortality observed with rifaximin over time. Furthermore, scenario analysis was undertaken to assess the impact of modelled mortality on the final ICER.
- Probabilistic sensitivity analysis was presented for a different range of scenarios.

Implications of the revised analysis

Revision of the additional evidence submitted by Norgine suggests that:

- The economic results are more robust when a lifetime time horizon is used as costs and benefits are appropriately captured.
- When the revised utility data and the lifetime time perspective are considered simultaneously in the economic analysis, the final base case ICER is **£28,805** per QALY.
- The revised utility values used in the economic analysis are a source of concern to the ERG:
    - The difference in utility assumed between rifaximin and placebo was derived using the adjusted utility analysis, however the ERG are concerned with the lack of detail and the validity of the analysis. More specifically there was not much detail around the methodology used to derive these values and p-values were not reported.
    - The utility value associated with the covert state in the placebo arm of the model is not sourced.
    - The difference in utility values assumed between the covert and the overt state in the model comes from the manufacturer's original submission, where utility values were taken from a study commissioned by Norgine and health state preferences were derived from the general public.
- The key driver of the cost-effectiveness results is the revised incremental utility assumed for rifaximin patients in the covert state compared with placebo patients in the covert state. The method used to derive such estimates raises some concerns. Therefore it is strongly recommended that clinical opinion is used to validate the utility gains claimed by the manufacturer.
- The incremental mortality benefit associated with rifaximin treatment compared with placebo is now in agreement with clinical reality as a diminishing benefit is observed over time. Furthermore, mortality is not likely to be a key driver of the final ICER and the modelled values are generally in accordance with real life data.
- Probabilistic sensitivity analysis showed that the revised utilities values used in the model are key drivers of the final ICER.

7.0 References

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