Addendum to Norgine NICE STA Submission on Rifaximin-α 550mg: Further Analyses in Response to Technology Appraisal Committee's Critique of the Economic Case

A Critique of the Addendum Submitted by Norgine

October 2013

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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. The Committee noted that the manufacturer's base-case ICER was £22,298 per QALY gained for rifaximin plus lactulose compared with placebo plus lactulose. 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.

The uncertainties in Norgine's original analysis were related with the following matters:

- Data from RFHE3001 and RFHE3002 were combined and used to model time to first HE episode. Using this dataset was thought to potentially introduce bias in the original analysis. Furthermore the distribution chosen to model time to event had a significant impact on the final results.
- Time to subsequent HE episodes was modelled as being independent of previous events. By assuming a constant risk for subsequent HE events, independent of the number of previous episodes and time spent in remission, the economic analysis was thought to depart from clinical reality.
- Time to death was modelled based on data from the literature, rather than trial data. The mortality in the economic model was considered to be an overestimation of the mortality observed in RFHE3001 trial and in clinical practice. Moreover most of the benefits in the model accrued from extended survival rather than improved quality of life (QoL), indicating that the estimated survival benefits of rifaximin were a major driver of the results.
- The utilities used in the model were derived from the general public in a study commissioned by the manufacturer. The Committee noted that the description used in the time trade-off approach was negatively worded and also included the probability of mortality, which could skew the results. It was also considered that the final utility estimates used in the model were too high, especially for people with underlying liver disease.

Following the NICE appraisal consultation process in June 2013, Norgine have submitted additional evidence and a revised cost-effectiveness model. In their revised submission, Norgine have presented new evidence suggesting that:

- The economic results are more robust with regards to the distributions chosen to model time to first and subsequent HE events.
- The economic results are more consistent with the clinical reality of subsequent HE events.
- The economic results are more consistent with the mortality rates observed in RFHE3001 and RFHE3002.
- Mortality is no longer the key driver of the final ICER, although it still contributes to generating significant QoL gains, and therefore has an impact on the cost-effectiveness analysis. Therefore clinical opinion should be used to validate the estimates.
- The key driver of the cost-effectiveness results is now the 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.

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 reflected a cost-effective use of NHS resources. The Committee noted that the manufacturer's base-case ICER was £22,298 per QALY gained for rifaximin plus lactulose compared with placebo plus lactulose. 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.

Following the NICE appraisal consultation process in June 2013, Norgine Pharmaceuticals have requested to submit additional analyses in relation to the appraisal of rifaximin-α (hereafter referred to as rifaximin) for the reduction in the recurrence of episodes of overt hepatic encephalopathy (HE) in patients 18 years of age and older. This request has been considered and agreed by NICE.

This document presents a critique of the additional evidence and the revised cost-effectiveness model submitted by Norgine in the Addendum to Norgine NICE STA Submission (hereafter referred to as the Addendum) as a response of the concerns highlighted by the Committee.

The remainder of this report is structured as follows:

- Section 2 presents a review of the updated literature searches.
- Section 3 is a description of the model structure.
- Section 4 is a review of the additional evidence presented for extrapolation of HE event data with a differentiation between the transition from covert to first HE episode and the transition from covert to subsequent episodes.
- Section 5 reviews the new utility values used in the revised model.
- Section 6 reviews the additional evidence relating to mortality.
- Section 7 concerns the review of the new assumption of the risk of hospitalisation.
- Section 8 refers to the results of the economic model.
- Section 9 concludes.

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

- Summary of first submission and Committee's comment
- Overview of method applied in the Addendum
- Critique of the method applied in the Addendum
- Implications

The implications sections provide an attempt to illustrate the impact on the ICER of each change made in the model. It should be noted however that comparing the impact of changing one parameter in the revised model with the original analysis can be challenging. The reason for this is that in the revised analysis, a significant number of changes were made to model parameters across different areas (for example, utility values, mortality rates, distributions used, etc.) and simultaneous changes in model parameters are driving the final results. Therefore the new ICER cannot always be directly compared to the original analysis. To the extent this proved to be possible, we have tried to isolate the effect of changing parameters across the original and the revised analysis. To this end, we present tables with the original ICER, the ICER obtained using the original value in the revised model and the

final ICER with the new value in the revised model (values in bold are the ones reported in Norgine's original and revised models). Thus, comparing the ICER obtained using the original value in the revised model and the final ICER enables showing the impact of changing one parameter at a time in the revised analysis.

2.0 Literature searches

Following the literature review included in the original submission, Norgine have carried out additional literature searches of:

- Clinical effectiveness
- Cost effectiveness
- QoL
- Mortality

These searches yielded no additional articles beyond those already identified.

Norgine have classified the searches as update searches, which would imply they updated the searches as previously submitted. The searches Norgine have provided in this re-submission are recorded as being run without a date limit (i.e. they do not appear to have been run from the date of the previous searches, or simply, a date limit was not applied to the search) and the volume the search yields, would suggest that the searches in fact, super-cede (both) the searches as previously submitted. If this is the case, the ERG is satisfied that these new searches for effectiveness, cost-effectiveness and QoL are fit for purpose.

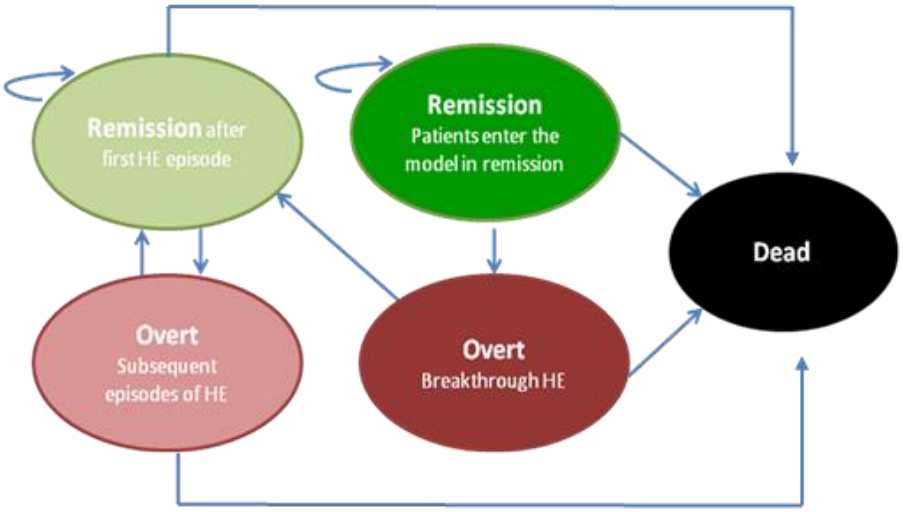
The ERG would like to underline the point made by Norgine that the targeted searches made for their report on mortality (Reynolds et al, 2013) are exactly that. They are not sensitive, and are not therefore potentially representative of the entirety of the literature in this field. The committee should be aware of the structural limitations of this targeted search (please refer to Appendix 1 for further details) but the ERG feels Norgine have been transparent about this through their clear, and systematic, representation of their targeted search strategy. Targeted searches to inform model parameters are widely used.

In their last submission, the ERG expressed concern that separate searches for adverse event data had not been carried out. Norgine have not addressed this point in their re-submission.

3.0 Description of model structure

Figure 1 shows the alternative representation of Norgine's economic model produced by the ERG on their original report (Bacelar et al, 2013). We found that this structure helps making clear the different transition probabilities between health states used in the model.

Figure 1. Alternative representation of Norgine's model produced by the ERG



In the original submission, Norgine assumed that the risk of a subsequent HE episode was independent of the risk of preceding episodes and the time spent in the remission state. Furthermore, the risk of a subsequent HE episode was modelled as a constant factor throughout the analysis.

The Committee and clinical specialists pointed to the fact that such assumptions were not an accurate representation of reality as the risk of subsequent events is dependent on having experienced previous events. The Committee also considered that more health states should have been included in the model to capture the complexities around the recurrence of subsequent hepatic encephalopathy episodes. The Committee concluded that the model structure oversimplified the nature and course of the disease.

Norgine did not change the model structure in their revised analysis. However, the risk of having subsequent HE episodes in the revised model was estimated based on data on time to subsequent events from RFHE3002. Subsequent events were considered as a single health state hence the probability of experiencing these was obtained for all subsequent HE episodes taken together.

This reveals an improvement in the sense that subsequent HE events were modelled as being time dependent and related to previous episodes. Nonetheless, subsequent HE episodes were considered as a unique event (i.e. cardinality of events was ignored in the analysis) thus modelled in a single health state.

To note is that the mortality risk in the revised analysis is modelled separately for first HE events and subsequent ones. This means that Norgine have also taken into account that the risk of mortality varies with the number of HE events (contrarily to the previous model).

4.0 Revised data inputs for extrapolation of HE event data

4.1 Combination of RFHE3001 and RFHE3002 data

In order to substantiate some of the decisions made to use new data inputs, Norgine undertook statistical analysis exploring the differences and similarities between the rifaximin arm of the RFHE3001 randomised controlled trial (RCT) and the three rifaximin treated subgroups in the RFHE3002 open-label trial (OLT). Subgroups from RFHE3002 were considered to be the following:

- Roll-over patients: subjects on rifaximin during RFHE3001 and kept on rifaximin for RFHE3002.
- Cross-over patients: subjects on lactulose during RFHE3001 who started rifaximin in RFHE3002.
- Rifaximin new patients: patients newly enrolled in RFHE3002.

In order to compare these populations and explore potential problems arising from combining them in the economic model, Norgine used unadjusted Kaplan-Meier (KM) plots of time to first HE event in all subgroups. Differences in KM survival curves were then explored with log-rank tests (Mantel-Haenzsel and Peto-modified Gehan-Wilcoxon statistics) using the null hypothesis that the survival curves between strata were the same. Alpha was set at 0.05 level.

Three separate analyses were presented:

- Comparison of time to first observed HE from RFHE3002 baseline for rollover, crossover and new patients (Figure 2).
- Comparison of time to first observed HE between RFHE3001 treatment groups and RFHE3002 subgroups, from each respective study at baseline (Figure 3).
- Comparison of time to first HE event between new rifaximin naïve entrants to RFHE3002 with the combined RFHE3001 and RFHE3002 data for rollover and crossover patients (Figure 4).

Figure 2 to Figure 4 show the results of the statistical analyses undertaken.

Survival curves shown on Figure 2 suggest a slight improvement in event-free survival (time to first HE) in the cross-over and roll-over patients compared with the new subject group. However, log-rank tests results of the difference in survival cures for new subjects and roll-over subjects revealed no statistically significant differences between survival in these groups (coefficients reported on Norgine's Addendum, p. 12).

The results of this analysis suggest that there were no significant differences between RFHE3002 subgroups in terms of time to HE events at 2 years after drug initiation.

Figure 2. Unadjusted KM plots of time to first HE event stratified by RFHE3002 subgroup (red, 3001 placebo crossover; green, 3002 new; blue, 3001 rifaximin rollover)

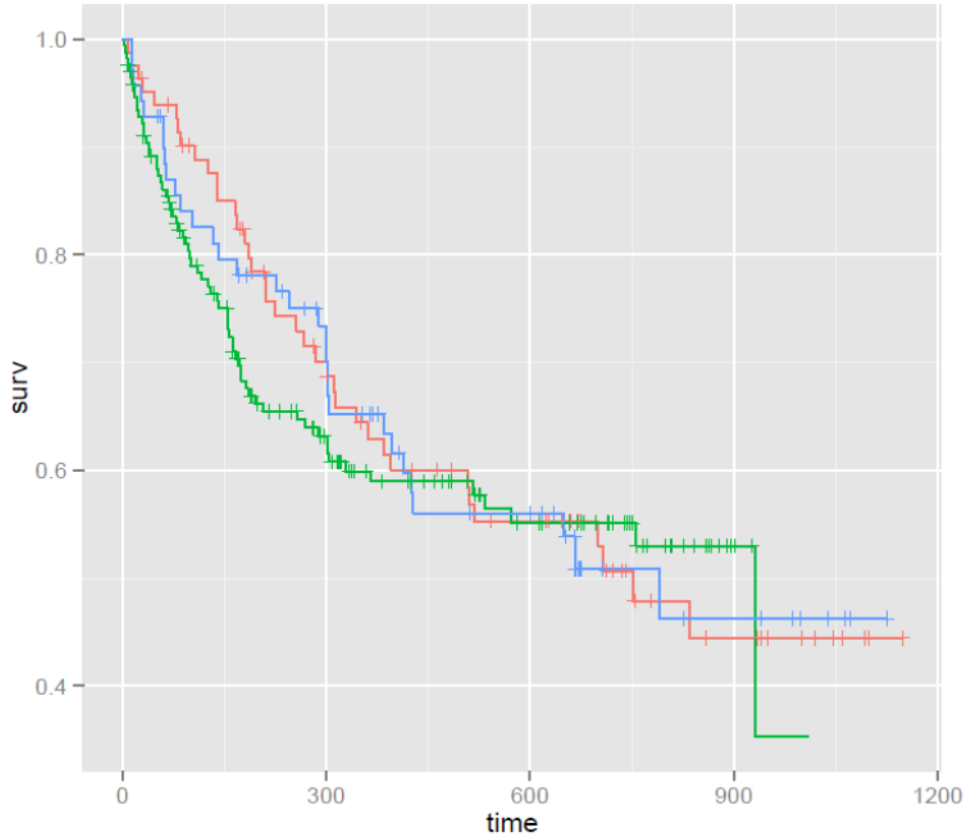
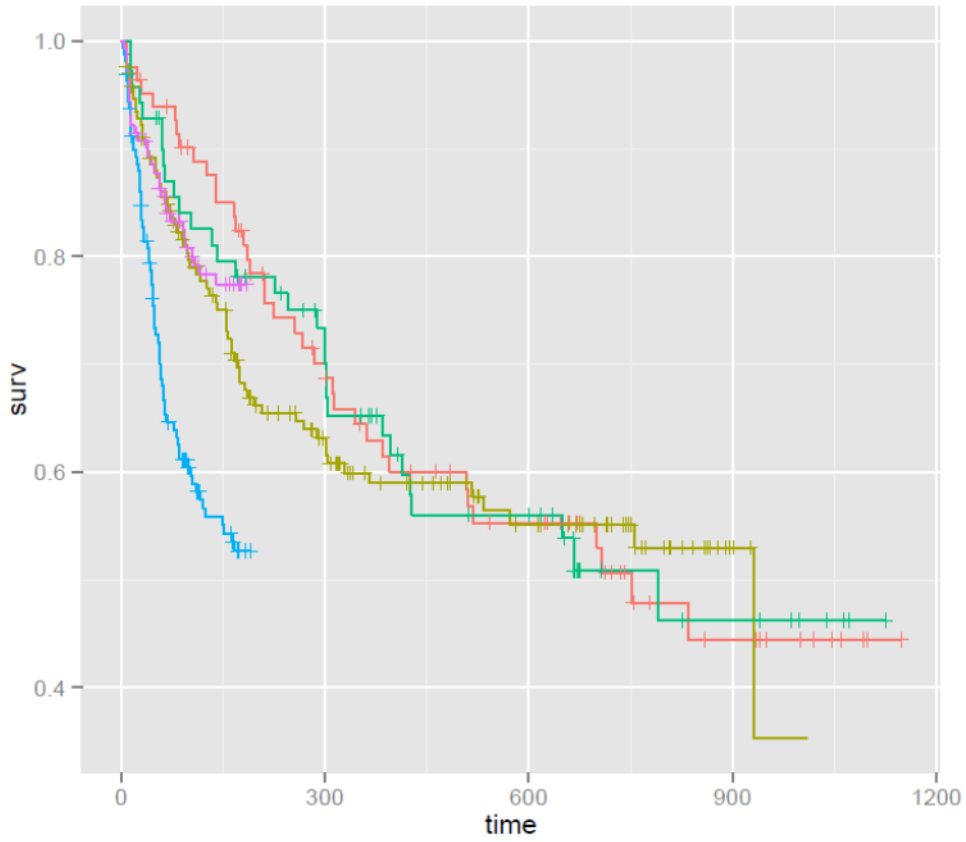


Figure 3 suggests that RFHE3001 rifaximin subjects and RFHE3002 are similar as the purple and the olive green curves seem to behave similarly throughout the initial 6 months when patients were on rifaximin (purple line representing rifaximin patients during RFHE3001 trial and olive green line showing new rifaximin patients during RFHE3002 study).

Log-rank tests (coefficients reported on Norgine's Addendum, p.13) between survival curves for patients treated with rifaximin during RFHE3001 and newly recruited patients treated with rifaximin during RFHE3002 showed that the null hypothesis that the curves are the same could not be rejected.

The results of this analysis suggest that there were no significant differences between RFHE3001 rifaximin and RFHE3002 newly recruited patients in terms of time to HE events at the end of RFHE3002 two-year analysis.

Figure 3. Unadjusted KM plots of time to first observed HE event stratified by RFHE3001 and RFHE3002 subgroup (blue, 3001 placebo; purple, 3001 rifaximin; olive green, 3002 new; red, 3002 placebo crossover; green, 3002 rifaximin rollover)



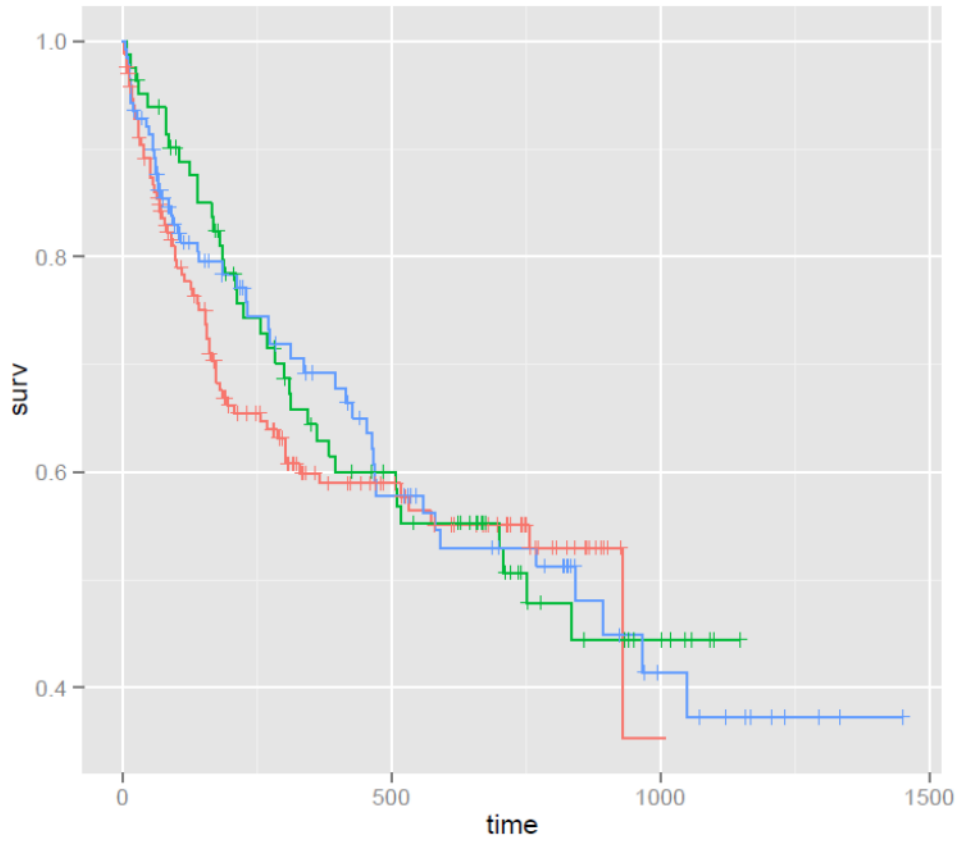
Finally, Figure 4 shows the unadjusted KM survival curves for new rifaximin patients on RFHE3002 study, along with the curves for cross-over and roll-over patients from RFHE3001 and RFHE3002 combined. All curves are from first rifaximin dose to censor/event date, therefore, roll-over rifaximin patients were followed during both RFHE3001 and RFHE3002.

Log-rank tests between survival curves for new subjects, cross-over subjects and roll-over subjects yield a $p > 0.05$, suggesting that the null hypothesis that the survival curves are the same cannot be rejected (coefficients reported on Norgine's Addendum, p.15).

The results of this analysis suggest that there were no significant differences between RFHE3002 newly recruited patients, roll-over and cross-over in terms of time to HE events at the end of RFHE3002 two-year analysis.

The statistical analysis reveals that by the end of RFHE3002 study (whether the analysis considered only RFHE3002 two-year time frame or the 6 months (RFHE3001) plus the 2 years in RFHE3002) the difference in time to HE event between RFHE3001 rifaximin patients and RFHE3002 subgroups is not statistically significant. The same conclusion can be drawn between RFHE3002 subgroups.

Figure 4. Unadjusted KM plots of time to first observed HE event stratified by RFHE3002 subgroup using combined RCT and OLT data (red, RFHE3002 new; green, placebo crossover [combined RFHE3001 & RFHE3002]; blue, rifaximin rollover [combined RFHE3001 & RFHE3002])



4.2 Transition from covert to first HE episode

Summary of first submission and Committee's comment

The original base-case analysis included modelling time to first HE episode by fitting parametric survival distributions to a dataset that combined RFHE3001 and RFHE3002 rifaximin patients. The Committee did not consider combining datasets to be appropriate because it broke randomisation and introduced bias, given that RFHE3002 did not include all patients from RFHE3001. Moreover, only data from RFHE3001 were used to model the placebo arm. The Committee noted that, despite this, distributions to extrapolate effectiveness data beyond the duration of the trial were chosen based on the combined dataset for both rifaximin and placebo arms. A log-normal distribution was fitted to the placebo arm of RFHE3001 and that the shape parameter from this regression was replaced by the shape parameter from the regression for the rifaximin arm. A substantial difference between the ICERs generated with the exponential and Weibull curves using the combined dataset (approximately £14,000 and £28,000 per QALY gained respectively, including the ERG adjustments) was noted. In contrast, when RFHE3001 data was used alone, the difference in the ICERs based on the two distributions was minimal (£20,230 and £20,102 per QALY gained for the exponential and Weibull curves, respectively), which further highlighted the uncertainties surrounding the use of the combined dataset. The Committee therefore concluded that only the RFHE3001 data should have been used to model both arms of the model (ACD, section 4.6)

Overview of method applied in the Addendum

Norgine used RFHE3001 data to model time to first breakthrough in both the rifaximin and the placebo arms of the economic model as per the Committee's advice. These data were extrapolated over 5 years using a log-normal distribution. Time to first HE was modelled using a proportional treatment effect assumption and survival times were right-censored at 170 days.

Critique of the method applied in the Addendum

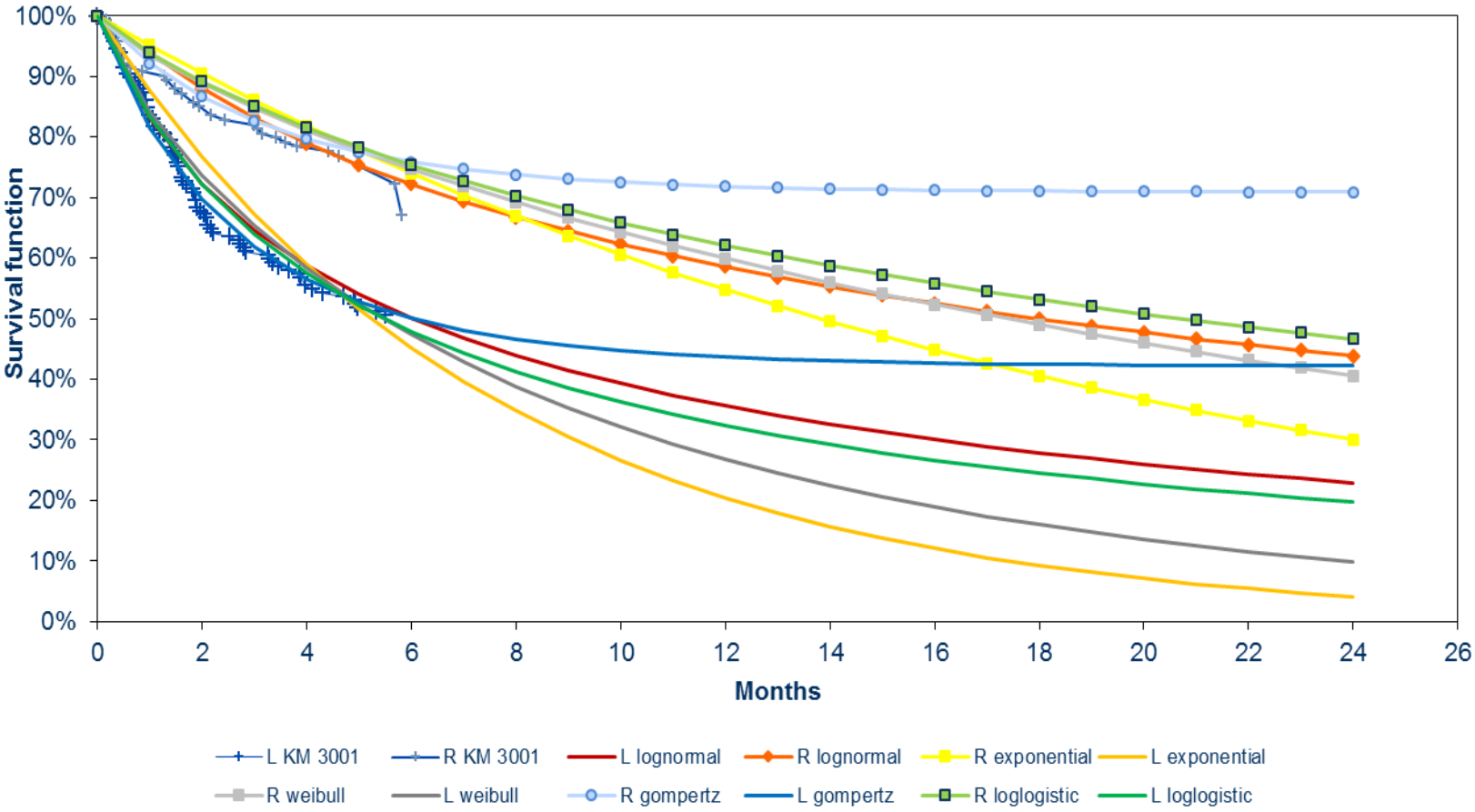
Norgine's approach departed from the original methodology used in that:

- Data from RFHE3001 alone were used to model time to first HE episode.
- Data censoring was undertaken at day 170 after treatment initiation, which differs from the original analysis where data censoring took place at day 168. The Clinical Study Report for RFHE3001 (CSR) states subjects who completed the study and did not experience a breakthrough overt HE event were censored at the time of their 6-month visit (which happened at day 170). It is not clear why Norgine have used two different points in time for censoring, when the CSR identifies censoring at day 170. Censoring patients at day 170 lead to different regression coefficients when extrapolating RFHE3001 data with different distributions.
- A proportional treatment effect between the treatment and placebo arms was assumed. This contrasts with Norgine's original approach which fitted both arms separately. This implies that, while in the original model no assumption was made as to the proportionality of the treatment effect, in the new analysis it is assumed that there is a constant acceleration factor (time ratio) over time. The validity of such assumption should have been assessed (for example, a quantile-quantile plot could have been used). Furthermore, assuming proportionality of the treatment effect also implies assuming patients will be kept on the drug until death. The clinical expert advising the ERG confirmed that HE patients are generally kept on rifaximin until death or liver transplant.

As in the original model, a log-normal distribution was used to fit RFHE3001 data. The decision was based on the log likelihood values for each distribution and visual assessment by fitting a semi-parametric Cox Proportional Hazard model and plotting the cumulative hazard function of the parametric and semi-parametric models for comparison). Further steps could have been taken to assess the goodness of fit of the different distributions. For example, it is not clear why the Akaike Information Criteria (AIC) or Bayesian Information Criterion (BIC) were not presented. Finally, the Gamma distribution should have been included in the analysis for the sake of completeness. The impact of using different distributions to model time to first HE episode is explored in the next subsection.

Figure 5 shows the KM curves of time to first HE episode for rifaximin and placebo patients in RFHE3001 as well as the survival curves obtained when different distributions are fitted to RFHE3001.

Figure 5. KM plots of time to first observed HE event from RFHE3001 and extrapolated survival curves over 2 years using different distributions



Implications

Censoring patients at day 170 results in different regression coefficients when extrapolating RFHE3001 data. This difference leads to different transition probabilities and subsequently different ICERs.

Table 1 shows the impact of changing the censoring day from 168 to 170. The original ICER obtained through the previous analysis with 168 days as the censoring point is shown in the second column. The third column shows the impact of using the old censoring point (168 days) within the revised current analysis. Finally, the last column shows the updated values with the most recent parameter used.

Using 170 days instead of 168 days as censoring point in the revised model decreases the final ICER by approximately £500.

Table 1. Overall impact of changing censoring day.

5-year analysis	Original analysis (combined dataset)	Revised analysis with original censoring point (RFHE3001)	Revised analysis with new censoring point (RFHE3001)
Difference in costs £ (rifaximin – lactulose)	£4,321	£11,101	£10,962
Difference in QALYs (rifaximin – lactulose)	0.1938	0.520	0.527
ICER	**£22,298**	£21,329	**£20,799**

Table 2 compares the final ICERs when different distributions are used to model time to first HE episode across the original analysis, the revised analysis with the original regression coefficients (i.e. censoring at day 168) and finally the revised model with the updated parameters (i.e. censoring at day 170).

As indicated in Norgine's Addendum, there is less variation across the ICERs depending on the choice of the distribution used, which brings more confidence in the ICERs presented.

Table 2. Overall impact of changing the distribution used to extrapolate data on time to first HE episode

5-year analysis	Extrapolation from RFHE3001 (Original model)	Extrapolation from RFHE3001 (Revised model with original censoring point)	Extrapolation from RFHE3001 (Revised model)
Exponential	£20,230	£20,137	£19,687
Weibull	£20,102	£19,405	£18,909
Gompertz	£27,139	£20,671	£19,504
Log-normal	[a] £25,017	£21,329	**£20,799**
Log-logistic	£23,164	£20,580	£19,383

a. In the original submission the ERG could not provide a robust value for this parameter as a mistake was found in Norgine model. However, with the data provided within the revised submission the ERG was able to correctly estimate this.

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4.3 Transition from covert to subsequent HE episodes

Summary of first submission and Committee's comment

The Committee was concerned about the plausibility of the manufacturer's assumption of a constant hazard for subsequent HE events applied in the original submission. It heard from the clinical specialists that a previous HE episode would increase the likelihood of subsequent episodes. The Committee considered that more health states should have been included in the model to capture the complexities around the recurrence of subsequent HE episodes. The Committee concluded that the model structure oversimplified the nature and course of the disease (ACD, section 4.5)

Overview of method applied in the Addendum

Norgine used data from open-label RFHE3002 study to model time to subsequent HE episodes as RFHE3001 did not collect data on subsequent episodes. However, only a specific subset of patients from RFHE3002 was used to model time to subsequent HE episodes – only the new rifaximin treated patients were included in the analysis. Data were extrapolated over 5 years using a log-normal distribution.

Event cardinality was not considered in the economic model, hence the log-normal distribution was fitted to the data on time to combined subsequent HE episodes in RFHE3002 (i.e. time to subsequent events was analysed together as a whole and not separately for each event).

Critique of the method applied in the Addendum

The primary aim of Norgine's approach was to make time to subsequent HE episodes dependent on experience of previous events.

Given that RFHE3002 was an open-label study with no control arm, the treatment effect for rifaximin compared with lactulose observed on RFHE3001 study was applied . Clinical advice sought by the ERG agreed this to be a reasonable approach.

The decision to take newly recruited rifaximin patients in RFHE3002 to model time to subsequent episodes was based on statistical analysis comparing time to first HE episode between RFHE3001 treatment group and RFHE3002 subgroups (rollover, crossover and newly recruited rifaximin patients) from each respective study baseline. This showed that time to first breakthrough in subjects treated with rifaximin in RFHE3001 and newly recruited subjects treated with rifaximin in RFHE3002 was not statistically different.

Norgine considered that using only new rifaximin patients in RFHE3002 avoids any potential enrichment bias. The ERG considers this to be a reasonable approach although, to some extent, it contradicts the approach taken in relation to mortality where the presence of no statistical difference between patient groups was used as an argument for using all three groups of patient data.

Contrary to the original model, a log-normal distribution was used to fit RFHE3002 data. Choice of the log-normal distribution was based on the log likelihood values for each distribution and visual assessment (by fitting a semi-parametric Cox Proportional Hazard model and plotting the cumulative hazard function of the parametric and semi-parametric models for comparison). Further steps could have been taking in assessing the goodness of fit of the different distributions. For example, it is not clear why the Akaike Information Criteria (AIC) or Bayesian Information Criterion (BIC) were not presented. Finally, the Gamma distribution should have been included in the analysis for the sake of completeness.

Figure 6 shows the KM curves of time to subsequent HE episodes for the new rifaximin patients in RFHE3002 as well as the survival curves obtained when different distributions are fitted to RFHE3002.

Figure 6. KM plots of time to subsequent observed HE event from RFHE3002 and extrapolated survival curves over 2 years using different distributions

The fact that time to subsequent HE episodes is now dependent of previous episodes is a significant improvement from the original submission where time to subsequent events was modelled as constant regardless of previous events. However, event cardinality has not been considered in the economic model. This to some extent ignores the Committee's requirement that more health states be considered to deal with the complexity of the disease progression. Instead, Norgine have combined all subsequent events and used one health state ($Covert_2$) to capture time to subsequent HE events in the economic model.

Implications

Table 3 compares the final ICERs in the original analysis and the revised model when different distributions are used to model time to subsequent HE events . Note that the original analysis used RFHE3001 data to model time to subsequent HE events by assuming that the risk of a subsequent event was constant over time, independent of previous events and independent of time spent in the remission state. The revised analysis uses data from RFHE3002 which captures time to subsequent events. Therefore, the values presented for the original model analysis do not hold much value.

Table 3 shows that changing the distribution used to model time to subsequent HE events carries some uncertainty (a concern previously highlighted by the Committee). However, with values ranging from £13,779 to £21,380 and the base case being £20,799 (log-normal distribution), the range is considerably narrower than in the original submission.

Table 3. Overall impact of changing the distribution used to extrapolate data on time to subsequent HE episodes

5-year analysis	Extrapolation from RFHE3001 (Original model)[a]	Extrapolation from RFHE3002 (Revised model)
Exponential	£25,017	£13,779
Weibull	£31,500	£15,830
Gompertz	£75,758	£19,872
Log-normal	£49,562	**£20,799**
Log-logistic	£46,633	£21,380

a. These values were obtained using RFHE3001 to model subsequent episodes. With the exception of the exponential distribution the resulting probabilities to subsequent event were not constant over time. Furthermore it should be noted that these values were obtained for the scenario were RFHE3001 extrapolated was used to model time to first HE episode in the original analysis.

5.0 Use of utilities in the cost-effectiveness model

Summary of first submission and Committee's comment

In the absence of preference-based measure of QoL, the utility values used in the original base-case analysis were taken from a study commissioned by Norgine where health state preferences were derived from the general public.

Quality of life data was collected in RFHE3001 using the Chronic Liver Disease Questionnaire (CLDQ) and SF-36, however Norgine chose to not use this data as it did not reflect the detriment in quality of life of HE events because patients were unable to rate their health during an overt episode; therefore the data collected only reflected the remission period. However, the Committee was aware that the SF-36 included a recall period and could potentially capture some of the impact of an overt episode.

The Committee was also concerned that the utilities estimated from the general public may not be reliable and were too high for people with underlying liver disease. The Committee concluded that it would be more appropriate to incorporate the QoL data collected from RFHE3001 in the model and any external data should only be used to supplement and validate this (ACD, section 4.6)

Overview of method applied in the Addendum

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. Rather than estimating final EQ-5D score directly, the algorithm predicts the ordinal response level to each of the five EQ-5D dimensions from the observed responses to the SF-12 subset of the SF-36.v1 questionnaire.

Exploratory analysis of the relationship between the observed overall CLDQ score and estimated EQ-5D index utility generated from the mapping exercise was performed with several regression analyses. Whilst the cubic and quadratic function have the higher explanatory power (R^2 = 0.590) the linear function is only marginally lower with 58.7% of variability in the EQ-5D explained by CLDQ overall score.

[redacted] modelling was used to quantify the relationship between overall CLDQ and estimated EQ-5D index utility: each additional unit CLDQ score confers an incremental utility of [redacted] utility.

Additionally, Norgine applied a utility increment to the baseline for the covert health state in the rifaximin arm. This increment was taken from the figure published in Sanyal et al (2011) 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 RFHE 3001 were used for this QoL analysis since there is no validated Russian translation of the CLDQ available.

The [redacted] parameter estimate for CLDQ was then applied to the baseline CLDQ score (4.11*[redacted], the incremental improvement in CLDQ score for rifaximin patients in the covert state (0.743 *[redacted]=0.106) and the CLDQ scores recorded in the overt state (3.76*[redacted].

Critique of the method applied in the Addendum

Following the Committee's recommendations, Norgine used QoL data collected from RFHE3001 in the revised model. The main observation that can be drawn from this approach is that the utility value associated to the covert health state of the rifaximin arm is now higher than the one associated to the covert health state of the placebo arm as seen in Table 4. In other words, the values now used imply that rifaximin offers a considerable QoL gain to patients in the covert state (and not just through prolonged time to HE events). This contrasts with the original model submitted by Norgine, in which QoL gains were exclusively linked to the difference in utilities between the covert and overt states.

Table 4. Mean utilities used in models by health states

Health state		Original utilities	Revised utilities
Covert	Placebo	[redacted]	[redacted]
	Rifaximin	[redacted]	[redacted]
Overt	Placebo	[redacted]	[redacted]
	Rifaximin	[redacted]	[redacted]
Difference (Covert minus Overt)	Placebo	[redacted]	[redacted]
	Rifaximin	[redacted]	[redacted]

It is not clear from the analysis presented in the Addendum why the utility values used in the model were drawn from the condition specific CLDQ and converted into EQ-5D when Norgine was able to map the generic health questionnaire SF-36 onto EQ-5D using a validated algorithm.

Mapping is a commonly used alternative to obtaining utility values from a generic or disease-specific health questionnaire when a preference-based measure is absent. Although the algorithm used to convert the observations from the generic questionnaire SF-36 was developed using a data set from the US general public and not from patients with liver cirrhosis, a correlation was demonstrated between the observed condition specific measures from the CLDQ and the estimated generic measures.

The treatment effect of rifaximin was derived from the longitudinal analysis using time-weighted averages of the CLDQ scores published by Sanyal et al (2011). The study showed an improvement in the overall CLDQ score. There is a certain level of uncertainty in the validity of the utility increment for two reasons:

- The first issue concerns the derivation of the incremental value since this was measured in centimetres directly from Figure 3 of the Sanyal et al (2011) publication, instead of using the actual values of differences in least square means.
- Secondly, the differences in least square means reported in Sanyal et al (2011) are as a result of CLDQ data collected for the whole duration of treatment until patients completed the study or withdrew due to breakthrough HE or other reasons. Norgine applied this utility increment between the rifaximin and placebo arms to the covert state only; the utility value for the overt state is the same for both arms. This approach is based on a strong assumption that the QoL gain measured by Sanyal and colleagues is due to treatment, and independent of the experience of HE events.

Implications

Table 5 shows the impact on the ICER of using the new utility values. As mentioned in the introduction it is challenging to evaluate the impact of changing only one parameter at a time since a significant number of changes were made between the original and the revised model. The second column shows the estimated ICER obtained through the previous analysis when using the original utilities, the third column shows the estimated ICER in the revised model using the original utilities, and finally the last column shows the updated analysis with the new utilities. Comparison of the two last columns shows the impact of the new utilities, which decreases the ICER from £38.246 to £20,799.

Table 5. Overall impact of changing utilities

5-year analysis	Original analysis	Revised analysis with original utilities	Revised analysis with new utilities
ICER	**£22,298**	£38,246	**£20,799**

Although Norgine did not present a Tornado diagram of their revised model, the utility values attached to the covert health states (rifaximin and placebo) seem to be one of the most influential drivers of the estimated ICER. In fact, Table 6 shows that when the same utility values [redacted] are applied to the treatment arm (i.e. QoL gains are only accrued through reduced recurrence of HE episodes and not through treatment itself) the ICER increases from £20,799 to £59,421.

Table 6. Impact of the utility increment on the ICER

5-year analysis	Revised analysis with new utilities	Revised analysis with new utilities (no increment between arms in the covert state)
ICER	**£20,799**	£59,421

6.0 Mortality

Summary of first submission and Committee's comment

The Committee considered the plausibility of the mortality estimated from the model. It noted that approximately 50% of the model population died over a 6-month period compared with 7% (21 deaths) in RFHE3001. It noted the manufacturer's statement that this was a result of the external data used to model the risk of mortality. The clinical specialists stated that mortality in the model was much higher than would be seen in clinical practice and that the mortality in the trial population would more closely reflect observed mortality.

The Committee was also concerned that the model predicted a 5% reduction in the risk of mortality with rifaximin compared with placebo during the first 6 months of the model and over the 5-year time horizon when there were no differences between the groups in RFHE3001. The clinical specialists suggested that a mortality risk reduction of 5% could be possible between treatment arms, although they acknowledged that there was no definitive evidence in the literature demonstrating a mortality benefit. The Committee noted that no differential mortality benefits between the treatment arms were apparent in the trial, and recognised that RHFE3001 was of short duration and that the manufacturer regarded the mortality data as being immature

It was also noted that most of the benefits in the model accrued from extended survival rather than improved QoL, indicating that the survival benefit with rifaximin was a major driver of the cost-effectiveness results.

The Committee concluded that the mortality estimates driving the results from the model were not robust (ACD, section 4.9).

The 5-year time horizon was considered to be appropriate because there was no robust evidence of a mortality effect; otherwise a life time horizon would be more appropriate (ACD, section 4.5)

Overview of method applied in the Addendum

Norgine undertook a targeted search strategy on the mortality of patients with HE, which also included an analysis of mortality data for HE patients using CPRD data. Mortality rates obtained through literature and CPRD data were then compared to the mortality rates on RFHE3001 and RFHE3002. Furthermore, statistical analysis was conducted 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.

All patients from RFHE3002 were included in this analysis, given a smaller number of deaths than HE events as per Norgine statement.

Time to death from the initial and subsequent covert states

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.

The index date for the initial covert state was the first open-label dose of rifaximin. For the subsequent covert state, the index was chosen as the 31st day following onset of the preceding HE event (i.e. when the model assumed the patent to return to the covert state). For patients whose next HE event occurred less than 30 days after the previous episode, the two neighbouring events were collapsed into a single event but maintained the 30-day recovery rule to set the index.

The choice of log-normal and Weibull distributions was based on assessment of log likelihood values. Model fit was also visually assessed by fitting a semi-parametric Cox Proportional Hazard model and plotting the cumulative hazard function of the parametric and semi-parametric models for comparison.

Probability of mortality within 30 days of the first and subsequent HE episodes (over 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 (□).

Critique of the method applied in the Addendum

Norgine did not justify why different approaches were taken to model mortality within the four health states. More precisely, no detail was given as to why survival analysis was used to model time to death from the covert states (initial covert and subsequent covert) while a simple proportion was calculated to estimate the probability of death in the overt states.

Furthermore, it was not demonstrated in any manner (neither in the Addendum report nor in the excel model) how the probability of death in both overt states was calculated. Presumably these were obtained as a ratio of the number of events (i.e. deaths) observed at the end of RFHE3002 for patients in the overt and the total number of patients in the overt state over the 2-year study period.

To model mortally inputs, all patients from RFHE3002 were included in the analysis. The ERG notes some inconstancy with this approach as Norgine included rollover patients which seems to somewhat contradict the efforts done with regards time to HE events (see Section 4) to step away from the potential enrichment bias.

Two different distributions (log-normal and Weibull) were used to fit RFHE3002 data. Further steps should have been taken in assessing the goodness of fit of the different distributions. For example, Akaike Information Criteria (AIC) or Bayesian Information Criterion (BIC) could have been presented. Finally the Gamma distribution should have been included in the analysis for the sake of completeness.

Even though Norgine used RFHE3002 data to model mortality in the economic model, KM curves were not provided on time to death from both covert states. Furthermore, the Excel model did not contain the necessary data to allow the ERG to plot such curves. Therefore, in this case, providing different distributions fitted to the RFHE3002 study mortality data would be meaningless as there are no KM curves for visual comparison.

One of the Committee concerns was the impact that mortality had on the original ICER. More specifically, the major benefits of the economic analysis were driven by mortality and not improvement in QoL.

Figure 7 and Figure 8 show that in the revised analysis, in a cohort of a 1,000 patients, after 5 years approximately 555 patients die in the placebo arm while approximately 480 die in the rifaximin group. This effect was obtained by extrapolating data from RFHE3002 on time to death for the covert state and taking the observed proportion of death in the overt state.

Figure 7. Markov trace diagram - placebo

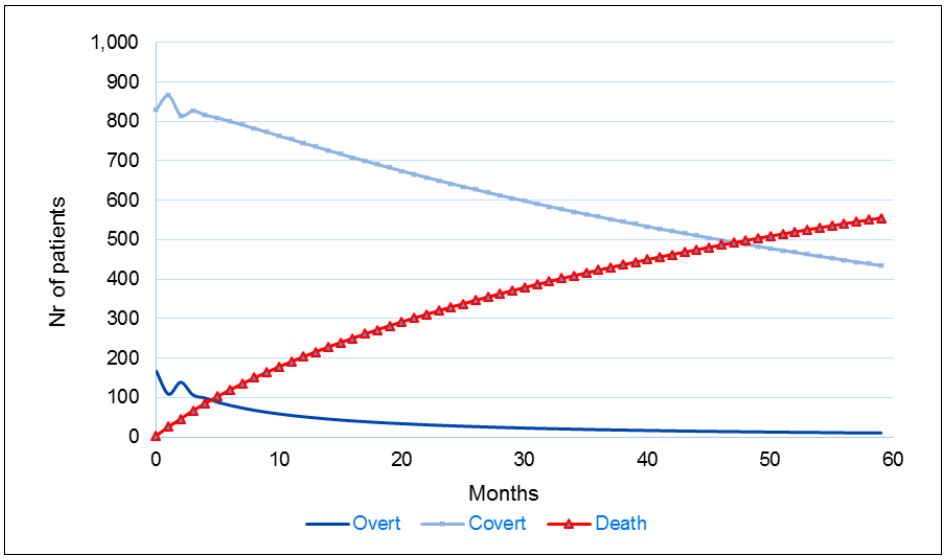
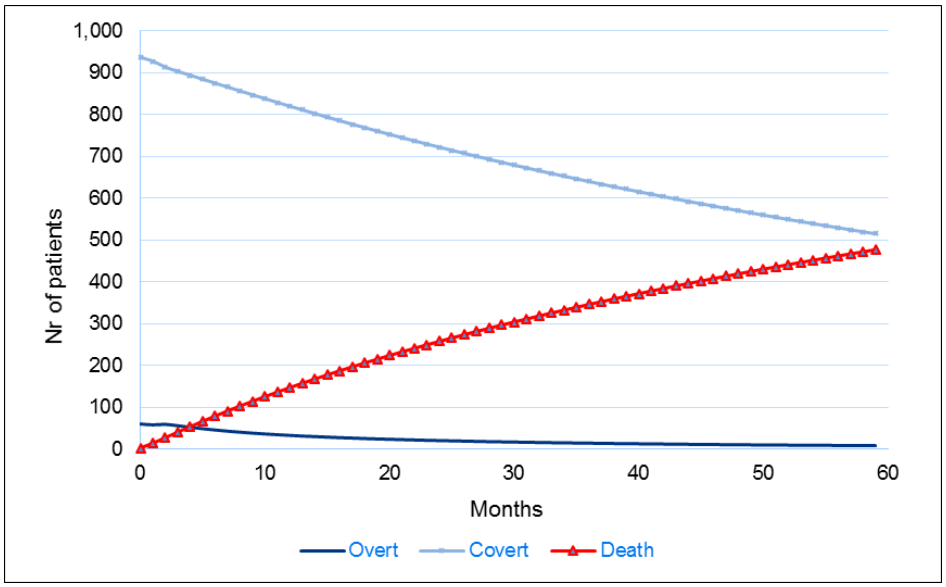


Figure 8. Markov trace diagram – rifaximin



Overall mortality in the placebo and in the rifaximin arm at year 5 show that approximately 55% of patients are death in the rifaximin arm while 45% remain alive in the placebo arm (Figure 9). As a substantial number of patients is still alive (and in line with the Committee initial view) a lifetime horizon should have been taken. Figure 10 shows the mortality curves if a lifetime approach had been taken. The resulting ICERs are presented in the next subsection. The graph shows that only after 35 years (approximately) the entire cohort is dead.

Even though mortality was modelled (partially) by extrapolating RFHE3002 data, Norgine did not present the KM curves for this mortality data. Such data would have been useful to allow comparison between the extrapolated curves.

Figure 9. Overall mortality over 5 years

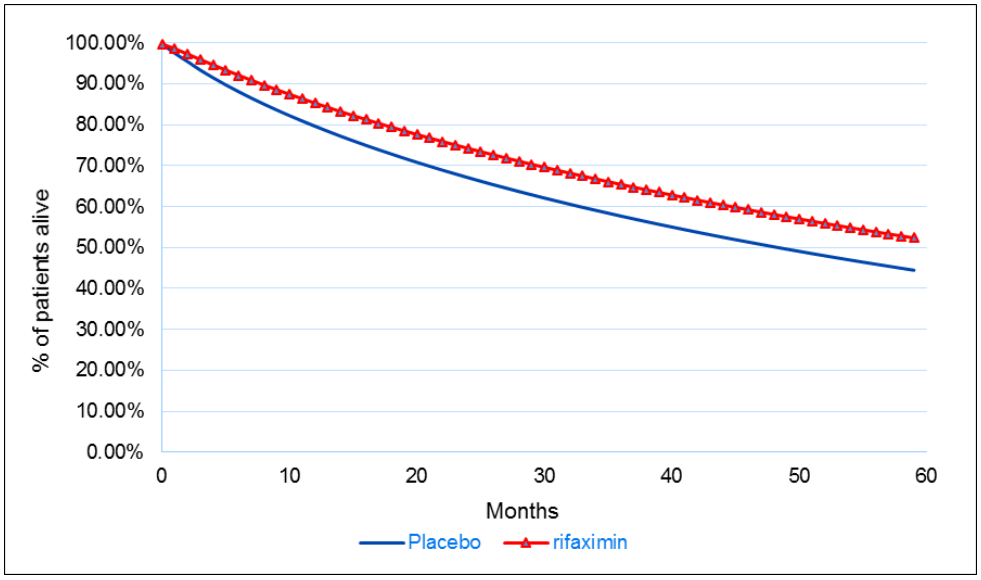
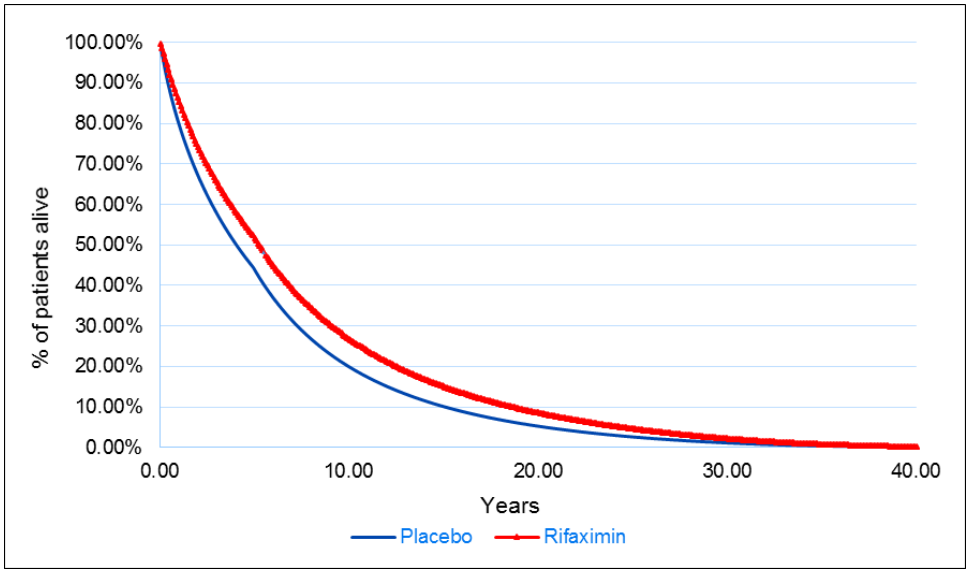


Figure 10. Overall mortality over lifetime (40 years)



Implications

Mortality rates

Table 7 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 death, 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 similar to that observed in RFHE3002. 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 at 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). Overall it was the clinical expert's opinion that the trial population is likely to reflect a healthier cohort than the standard HE patient group.

Table 7. Mortality rates from different sources (Addendum, p.41)

Mortality	1 mnth	6 mnths	1 year	2 years	3 years	4 years	5 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%	6.68%	13.67%	24.95%	33.91%	41.35%	47.66%
Lactulose	0.29%	10.28%	19.11%	32.01%	41.61%	49.25%	55.53%

ICERs

In the revised model the impact of mortality on QALYs gained is considerable lower than in the original one. Nevertheless, it still is a significant component of the analysis. Table 8 shows the impact of mortality on the final revised ICER. It shows that the modelled mortality on the covert states has a reasonable impact on the final ICER. When the benefits in covert mortality are excluded from the analysis the final ICER goes from £20,799 to £22,700. As expected, however, it is the mortality in the overt states that has a larger effect on the final ICER. When deaths avoided are no longer considered

in the overt states, the final ICER goes from £20,799 to £26,120. Overall, when no mortality benefits are considered at all, the final ICER goes up to £30,200.

Table 8. Impact of mortality decomposed

5-year analysis	Revised mortality inputs	Mortality in the covert state excluded (overt mortality included)	Mortality in the overt state excluded (covert mortality included)	Mortality excluded from the model
ICER	**£20,799**	£22,700	£26,120	£30,200

Finally, the ERG estimated the final ICER if a lifetime perspective was to be adopted. The results are presented in Table 9. Compared with the 5-year ICER of £20,799, the lifetime (40 years) estimate shows only a £1,270 improvement which suggests that the major benefits associated with rifaximin happen during the initial years of treatment.

Table 9. Lifetime ICER

Cost-effectiveness results per patient	Rifaximin (1)	Placebo (2)	Incremental value (1-2)
Total costs £	£27,124	£6,479	£20,644
QALYs	3.917	2.981	0.935
ICER			£22,069

7.0 Hepatic encephalopathy-related hospital admissions

Summary of first submission

The original base-case analysis assumed a differential HE-related hospitalisation rate between rifaximin-α 550mg and placebo as observed in RFHE3001. In the original model the 6-month probabilities of hospital admission (36/73 [49.32 %] vs. 19/31 [61.29%] for the placebo arm and rifaximin arm, respectively) were converted to monthly probabilities of 10.71% vs. 14.63% respectively assuming a constant hazard of hospitalisation over time. These monthly probabilities were applied to the cost of weighted average cost of hospitalisation in order to calculate the cost of patients in the overt state in both arms.

Overview of method applied in the Addendum

In the Addendum Norgine suggested that further review of the data demonstrated this approach to under-predict the number of HE-related hospitalisation and that the difference in proportion is not statistically insignificant. Therefore, a single constant risk of hospitalisation has been used in both arms within the revised model. The reasons for this change were twofold:

- Firstly, Norgine compared the HE-related hospitalisation predictions from the original model to the ones observed in RFHE3001. When the monthly probabilities are applied to the patients predicted to reach the overt state in the model, the predicted number of HE hospitalisation is much lower than the ones observed in RFHE3001: 8 vs. 36 and 5 vs. 19 hospitalisations for the rifaximin arm and placebo arm, respectively. However when the 6-month probabilities are applied to the patients predicted to reach the overt state in the model for each month, the predicted number of HE hospitalisations is close to the ones observed in RFHE3001: 37 vs. 36 and 21 vs. 19 hospitalisations for the rifaximin arm and placebo arm, respectively.

- Secondly, the two-tailed z-test showed that the number of patients hospitalised because of HE events observed in RFHE3001 were not statistically different between the two arms. There was an overlap between the two 95% confidence intervals given the small number of events.

For the two reasons detailed above, Norgine have considered that applying the aggregated 6-month probability of 52.88% to both arms is a more appropriate assumption.

Critique of approach used

The comparison of the predicted and observed numbers of HE-related hospitalisations presents a good rationale for applying the 6-month probabilities rather than the monthly probabilities. In addition, appropriate justification was presented by Norgine to not refute the null hypothesis of the two proportions being equal. However, the use of the aggregated proportion was not supported by clinical opinion and the ERG encourages seeking clinical advice from members of the Committee on the validity of this assumption.

Implications

Table 10 presents the impact of using different hospitalisation probabilities on the cost per HE event and the ICER. It should be noted that the cost of an HE event used in the revised model is different from that in the original model not just due to the change in hospitalisation rates described above but also given that Norgine considered that the cost of an outpatient attendance associated with non-

hospitalised HE events had been incorrectly specified in the original submission. The DoH Tariff applied to outpatient attendances changed from £110.68 (Clinical haematology, Service code 303) in the original submission to £176.27 (Hepatology, Service code 306) in the revised submission.

The results of changing hospitalisation rates and the cost of an outpatient attendance show that:

- When applying the monthly probabilities (10.71% and 14.63%) the cost of an HE event increases from £293/£360 in the original model (placebo and rifaximin respectively) to £359/£425 in the revised model. The ICER in the original model was £22,298. We do not report the ICER in the revised model, as Norgine considers these probabilities to be incorrect.

- When applying the 6-month probabilities (49.32% and 61.29%) the cost of an HE event increases from £950/£1,154 in the original model (placebo and rifaximin respectively) to £1,016/£1,220 in the revised model. This leads to a small increase of the ICER from £20,774 in the original model to £21,389 in the revised model.

- When applying the aggregated 6-month probability of 52.88% to both arms, the cost of an HE event increases from £1,011 in the original model to £1,077 in the revised model. This leads to a decrease of the ICER from £22,937 in the original model to £20,799 in the revised model.

The position of the ERG is that, even if the two proportions of HE hospitalised are not statistically different, the conservative assumption would be to use the two different probabilities observed for each arm respectively as the aggregated probability risks underestimation of hospitalisation for the rifaximin arm. This assumption increases the ICER from the base case presented in the Addendum (£20,799) to £21,389.

Table 10. Impact of hospitalisation probabilities on HE event costs and ICER

Hospitalisation probabilities used	Cost of HE event (placebo/rifaximin)		ICER	
	Original model	Revised model	Original model	Revised model
Different monthly probabilities: 10.71% and 14.63%	£293/£360	£359/£425	**£22,298**	-
Different 6-month probabilities: 49.32% and 61.29%	£950/£1,154	£1,016/£1,220	£20,774	£21,389
Aggregated 6-month probability: 52.88%	£1,011	£1,077	£23,543	**£20,799**

8.0 Economic modelling results

Base case

The revised cost-effectiveness analysis of rifaximin-α 550 mg for the prevention of recurrence of HE in patients with liver cirrhosis presented an ICER of £20,799 over 5 years. This represents an overall reduction of £1,499 per QALY over the base case analysis in the original submission with the corrections made by the ERG (£22,298).

Table 11. Cost-effectiveness results in the revised analysis

Cost-effectiveness results per patient over 5 years	Rifaximin (1)	Placebo (2)	Incremental value (1-2)
Total costs £	£15,522	£4,561	£10,962
QALYs	2.356	1.829	0.527
ICER			**£20,799**

Sensitivity analysis

Norgine's sensitivity analysis was limited to the use of alternative extrapolation curves for first and subsequent HE events, extrapolation curves for covert mortality, and utilities. No other sensitivity analyses were provided in the Addendum. Similarly, the Addendum did not provide probabilistic sensitivity analysis or sub-group analysis.

Time to HE events

Compared with the original submission, the analysis presented in the Addendum shows less variation across ICERs when different distributions are used to model time to HE events. This conclusion holds for time to first event as well as time to second event.

Table 12 shows the ICER estimates when different distributions are used to model time to HE events over a 5 year period. Column 2 shows the ICERs resulting from the original cost-effectiveness analysis where RFHE3001 and RFHE3002 data combined were used to model time to first HE episode with different distributions. Column 3 shows the same estimates when only RFHE3001 data were extrapolated in the original analysis. Finally column 3 and 4 present the ICERs resulting from the revised cost-effectiveness analysis, when the distribution used to model time to first HE event and time to subsequent HE event are used, respectively.

Comparing the results from the original analysis (columns 2 and 3) with the revised analysis (column 4 and 5) shows that the choice of the survival distribution now has considerable less impact on the resulting ICERs. Therefore, the ERG agrees with Norgine in that the revised model produces more stable cost-effectiveness estimates than the original model.

Table 12. Cost per QALY for a 5-year analysis – original vs. revised model

5-year analysis	Extrapolation from RFHE3001 and RFHE3002 (Original model)	Extrapolation from RFHE3001 (Original model)	Extrapolation from RFHE3001[a] (Revised model)	Extrapolation from RFHE3002[b] (Revised model)
Exponential	£14,438	£20,230	£19,687	£13,779
Weibull	£27,825	£20,102	£18,909	£15,830
Gompertz	£13,740	£27,139	£19,504	£19,872
Log-normal	[e] **£22,298**	[d] £25,017	**£20,799**	[c] **£20,799**
Log-logistic	£21,006	£23,164	£19,383	£21,380

a. Showing the effect of varying the survival distribution of the first HE transition whilst assuming a log-normal distribution for subsequent transition from covert to overt.
b. Showing the effect of varying the survival distribution of subsequent HE transitions whilst assuming a log-normal distribution for first HE event.
c. The result shown in this box is the same as that for the standard extrapolation for log-normal. Log-normal distribution has been used for both the 1st and 2nd phase of the model.
d. Corrected value provided by ERG
e. This ICER corresponds to the base-case value with the corrections made by the ERG (ERG Report)

Norgine presented ICERs for a 10-year time frame. The ERG found some (small) discrepancies between the estimates presented in the Addendum (Table 15, p. 47) and those in the Excel model. It was not possible to identify the source of the problem. Using the estimates in the Excel model, Table 13 shows that:

- When a 10-year analysis is considered, the estimated ICERs are generally higher in the revised analysis than in the original analysis, with the exception of two cases (when the exponential or the Weibull distribution are used instead of the log-normal distribution to model time to subsequent events).
- In the revised model (and contrary to the original model) changing the time horizon from 5 years to 10 years tends to increase the estimated ICERs. As pointed out by Norgine this is likely to be a result of the mortality curves used.

Table 13. Cost per QALY for a 10-year analysis – original vs. revised model

10-year analysis	Extrapolation from RFHE3001 and RFHE3002 (Original model)	Extrapolation from RFHE3001 (Original model)	Extrapolation from RFHE3001[a] (Revised model)	Extrapolation from RFHE3002[b] (Revised model)
Exponential	£11,380	£15,652	£22,373	£12,917
Weibull	£19,143	£15,065	£20,829	£14,755
Gompertz	£10,482	£21,144	£21,699	£23,603
Log-normal	£16,546	£18,248	£22,987	£22,987
Log-logistic	£15,705	£17,212	£21,099	£24,495

a. Showing the effect of varying the survival distribution of the first HE transition whilst assuming a log-normal distribution for subsequent transition from covert to overt.
b. Showing the effect of varying the survival distribution of subsequent HE transitions whilst assuming a log-normal distribution for first HE event.

Adding to the analysis presented by Norgine, the ERG has calculated lifetime ICERs using a time horizon of 40 years. This corresponds to following the cohort of patient until they reach 100 years of age. By year 40, nearly 100% of patients are dead in both the rifaximin and the placebo arms of the model.

Table 14 shows that when a lifetime horizon is considered, the ICERs either increase or decrease (compared with the 10-year analysis), depending on the distribution used. The same applies when lifetime ICERs are compared with 5-year ICERs. In general though, the estimates do not present major differences when different time horizons are used for the economic model. It should be noted that in the original analysis, when wider time frames were adopted, the ICERs consistently decrease with time and across the different distributions.

Table 14. Cost per QALY for a lifetime analysis – original vs. revised model

Lifetime analysis (80 years)	Extrapolation from RFHE3001 and RFHE3002 (Original model)	Extrapolation from RFHE3001 (Original model)	Extrapolation from RFHE3001[a] (Revised model)	Extrapolation from RFHE3002[b] (Revised model)
Exponential	£10,536	£14,432	£23,108	£12,441
Weibull	£15,777	£13,693	£21,070	£13,504
Gompertz	£8,985	£18,609	£20,792	£24,714
Log-normal	**£14,144**	**£15,908**	**£22,070**	**£22,070**
Log-logistic	£13,561	£15,214	£20,149	£24,441

a. Showing the effect of varying the survival distribution of the first HE transition whilst assuming a log-normal distribution for subsequent transition from covert to overt.

b. Showing the effect of varying the survival distribution of subsequent HE transitions whilst assuming a log-normal distribution for first HE event.

Covert mortality survival distribution

Norgine undertook sensitivity analysis of the extrapolation curves for covert mortality, even though it was not clear in the Excel model how this analysis was run or how the model parameters were varied in this analysis.

As a result of the sensitivity analysis, Norgine claims that the choice of survival distribution used to model mortality from the covert state does not have a significant impact on the final ICER (£19,796 to £21,630). However, it should be noted that the choice of distributions for extrapolated mortality data was poorly substantiated.

The ERG has shown that mortality is still a significant driver of the final ICER, as excluding all the mortality benefits from the economic analysis would drive the final ICER up to £30,200.

Utilities

Norgine points to the incremental utility used in the rifaximin arm as having some impact on the final ICER (with values ranging from £13,859 to £41,663, for the upper and lower limit of the confidence interval of the utility attached to the covert state in the rifaximin arm).

The ERG has shown that the incremental utility used in the covert state is the major driver of uncertainty in the final ICER, with the latter picking to £59,400 when the same utility value is considered for the covert state in both the rifaximin and the placebo arms.

9.0 Conclusion

Having considering the original submission made by Norgine, the Committee concluded that the ICER resulting from the analysis (£22,298) 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 original economic analysis, 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 original analysis

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

- Data from RFHE3001 and RFHE3002 were combined and used to model time to first HE episode. Using this dataset was thought to potentially introduce bias in the original analysis. Furthermore the distribution chosen to model time to event had a significant impact on the final results.
- Time to subsequent HE episodes was initially modelled as being independent of previous events. By assuming a constant risk for subsequent HE events, independent of the number of previous episodes and time spent in remission, the economic analysis was thought to depart from clinical reality.
- Time to death was modelled based on data from the literature, rather than trial data. The mortality in the economic model was considered to be an overestimation of the mortality observed in RFHE3001 trial and in clinical practice. Moreover most of the benefits in the model accrued from extended survival rather than improved quality of life (QoL), indicating that the estimated survival benefits of rifaximin were a major driver of the cost-effectiveness results.
- The utilities used in the model were derived from the general public in a study commissioned by the manufacturer. The Committee noted that the description used in the time trade-off approach was negatively worded and also included the probability of mortality, which could skew the results. It was also considered that the final utility estimates used in the model were too high, especially for people with underlying liver disease.

Norgine's approach in the revised analysis

In their revised analysis Norgine have taken the following steps:

- Data from RFHE3001 was used to model time to first HE event. RFHE3002 was excluded from this particular analysis.
- Time to subsequent HE episodes was modelled using RFHE3002 data. In the revised analysis, the risk of subsequent episodes is dependent on previous episodes and is no longer constant over time. However, subsequent events were taken as a whole and modelled accordingly.
- Mortality rates were estimated using RFHE3002 data. Different modelling methods and death probabilities were used/obtained depending on the health state of the model (initial overt, subsequent overt, initial covert, subsequent overt).
- Utilities in the revised model were gathered by mapping SF-36 observations collected in RFHE3001 to EQ-5D utility values, and converting improvements in CLDQ scores to utility gains. Norgine applied a utility increment to the baseline for the covert health state in the rifaximin arm.

Implications of the revised analysis

In their revised analysis Norgine presented new evidence suggesting that:

- The economic results are more robust with regards to the distributions chosen to model time to first and subsequent HE events.
- The economic results are more consistent with the clinical reality of subsequent HE events.
- The economic results are more consistent with the mortality rates observed in RFHE3001 and RFHE3002.
- Mortality is no longer the key driver of the final ICER, although it still contributes to generating significant QoL gains, and therefore has an impact on the cost-effectiveness analysis. Therefore clinical opinion should be used to validate the estimates.
- The key driver of the cost-effectiveness results is now the 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.

10.0 References

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11.0 Appendix 1: Literature searches

Mortality searches

Norgine have used EMBASE.com as their host platform for their MEDLINE and EMBASE searches for these targeted mortality searches. At this time, Embase.com does not include MEDLINE In Process references, so the searching here is not as current as it would have been had they used MEDLINE (OVID) (as they have for their other searches) or PubMed in addition to EMBASE.com. In principle, this means they may have missed more recent publications, as they have come into the National Library of Medicine. Their searching for this report on mortality is also now four months old.

Norgine have used the term 'targeted' literature search so as to differentiate between a full systematic and sensitive search. They have used free-text terms for outcomes and run these against (Emtree) index terms for HE and liver cirrhosis populations. In principle, and bearing in mind the targeted nature of these searches, this is acceptable. There are, however, risks when relying solely on index terms as they have. These include:

- Indexing terms are only assigned to records if it is clear that the record in question relates to the index term of choice. If the title/abstract is not clear, and/or a reference to HE (for example) is only brief in the abstract, the assignation of indexing terms might not be made comprehensively, and so a paper might be missed, miss-indexed or assigned an alternative indexing term. In this case, Norgine's decision to limit their searching to population index terms (only) may have led them to miss items. Using free-text search terms (in addition to index terms) would have countered this issue but might have impinged on specificity.

- They have used major heading terms (mj) to focus their population search terms. I assume this has been done for precision (i.e. to locate only references which are explicitly about (or majority about) HE rather than only making reference to HE.) This reflects their aim for a targeted search, so it is not also sensitive. As above, an error of indexing assignment could have been made, causing a record to be missed. References where HE is a part of a broader point (for example, perhaps a record discussing HE amongst other points) might not be indexed as an MJ heading but might still provide relevant outcome data, which would have been missed.

- Their use of free-text terms (for outcomes) does not include truncation so their searches would have only returned the specific words they have used. This might be fine as it likely has been designed to reflect the targeted nature of their searching.

- Their searches are limited to human only populations and to English language studies. The latter is in keeping with NICE methods but the way they have executed the exclusion to human populations does not appear to be consistent with advice by groups such as the Cochrane collaboration. The Cochrane Handbook recommends running a very specific search line to exclude animal populations. This is because the limits the database relies upon run differently to the lines as advised by Cochrane. The efficacy of the database limits (as compared with the Cochrane limits) is doubtful and could lead to the accidental removal of includable studies.