Norgine Response to Rifaximin NICE ACD

No	Section of ACD	Page No	Relevant Text	Norgine's Comments
1.	Cost-effectiveness evidence: 3.15	12	*All patients enter the model in the remission state…*	An exploratory analysis of the baseline data from RFHE3001 is being undertaken in order to better understand the patients' prior disease. This will also help to describe the state of decompensated disease at the start of the cost effectiveness model. Furthermore, in collaboration with clinical opinion leaders, Norgine has initiated an analysis of UK patient databases to better understand the use of rifaximin-α in UK patient populations. This data has only recently become available to Norgine (after the initial submission to the NICE)
2.			*….and in each cycle, patients can remain in remission, progress to the overt state (breakthrough and subsequent episodes that may include hospital admission), return to the remission state from the overt state or progress to the dead state from the remission or overt states*	Data from RFHE3001 is being explored to better describe the disease states after a series of episodes of overt HE. Norgine believe via consultation with clinical experts that the current economic model has not captured the disutility from multiple episodes of HE and the resource consequence associated.
3.			*The model had a time horizon of 5 years consisting of monthly cycles, did not include a half-cycle correction*	Norgine believes that the month cycle assumption is reasonable to best describe the progression of disease. The appropriateness of a half cycle could be considered when the analysis of the new external UK patient data, now available to Norgine is undertaken.
4.	Cost-effectiveness evidence: 3.16 (see also 4.3, page 30 and 4.6, page 32-33)	13	*A separate Kaplan-Meier plot of time to first breakthrough episode of hepatic encephalopathy was available for rifaximin-α patients who were in remission at the end of the 6-month RFHE3001 study and elected to join the RFHE3002 open label extension study.*	Norgine is exploring the RFHE3002 trial data to better understand the data related to all new patients initiated in this open label extension study. Data from the rifaximin -α patients in RFHE3001 were previously the only data included in the Kaplan-Meier plots and subsequent statistical curve fit analysis. Norgine accept that this may have led to a misinterpretation of the subsequent economic model, but believe the data on all patients in the RFHE3002 trial should be considered at least in the form of sensitivity analyses to better describe the morbidity and mortality progression beyond the first 6 months of rifaximin-α and lactulose therapy.
5.			*The survival curves were then extrapolated beyond 168 days for both groups using a log-normal distribution, which the manufacturer considered to provide the best model fit based on Akaike and Bayesian information criteria and visual inspection.*	Norgine believes that further examination of the total patient pool in the RFHE3002 open label extension study should be used to better understand the morbidity and mortality progression for HE patients. The use of fitted curves to the RFHE3001 data alone has limitations and we believe that the RFHE3002 data can be used to help support the extrapolation analysis. Norgine would like to present further sensitivity analyses to support this approach.

6.	Cost-effectiveness evidence: 3.17 (see also 3.38, page 25)	13	*Given that time to subsequent episodes was not available from RFHE3001, the manufacturer assumed that the risk of having a subsequent breakthrough episode was independent of the risk of preceding episodes and the time spent in the remission state. It was also assumed that the risk reduction for the first breakthrough episode could also be applied to subsequent episodes, based on clinical expert opinion, and this was assumed to be constant over time for subsequent episodes.*	Norgine is exploring the RFHE3002 open label extension study and the new observational patient data recently made available to explore these issues. The RFHE3001 trial did not provide an opportunity to analyse or explore these issues, and conservative assumptions were taken in the current submitted version of the model. Additionally, this approach does not adequately underline that disease progression is linked to contributing / precipitating factors that rifaximin could reduce (for example, bleeding, infections, spontaneous peritonitis).
7.	Cost-effectiveness evidence: 3.18	14	*Hepatic encephalopathy-specific mortality was estimated from other external data sources (Bustamante et al. 1999 and Shawcross et al. 2011) rather than the RFHE3001 data. <u>The manufacturer stated that this was because the trial population did not reflect the range of patients who would present with hepatic encephalopathy in clinical practice</u>*	The underlined statement is incorrect. Please refer to our submission Section 7.3.1, page 99, last 2 paragraphs: *'There is also evidence to suggest that patients who experience HE face a higher mortality risk than patients without HE, the mortality risk increases further with more severe grade of HE (12, 14, 18-20). It is plausible that reducing the recurrence of HE, as is associated with rifaximin treatment could result in improved overall survival. Mortality data from RFHE3001 were not sufficiently mature to address the impact of rifaximin on survival.* *Whilst the study population reflects patients with HE seen in common clinical settings (District General Hospitals), it doesn't provide evidence for patients at the more severe end of the disease spectrum. In the economic analysis rather than using the RCT data on mortality, data are taken from other sources Bustamante et al, 1999 and Shawcross et al, 2011 (12, 14) to reflect the whole range of patients who would present with HE in clinical practice.'* For further clarity, RFHE3001 was 6 months in duration. Thus, the data was not sufficiently mature enough for mortality analysis. Norgine stated that the trial population did reflect patients seen in clinical practice with HE, as a result of chronic liver disease (cirrhosis). There was a mix of patients with cirrhosis related to alcohol and viral hepatitis for example. This is representative of the most common aetiology of the underlying liver disease seen in clinical practice. In addition, the inclusion criteria ensured that patients with HE were in line with patients seen in clinical practice.
8.	Cost-effectiveness evidence:	16	*The hospital admission costs used in the model were estimated using NHS reference costs for*	Norgine is currently undertaking a review of observational data which has recently become available to explore the actual use

	3.22		*2011/12 and were based on the monthly average from RFHE3001 (14.63% and 10.71%, rifaximin-α and placebo) and a mean length of stay of 5 days*	of rifaximin-α in UK practice and its effects on resource use in the NHS
9.	Cost-effectiveness evidence: 3.30	20	*The ERG stated that the evidence submitted by the manufacturer generally reflects the decision problem adequately even though the population and comparator differed from those specified in the final scope. Whereas the scope referred to adults who have had episodes of hepatic encephalopathy, the manufacturer's submission only considered adults with chronic liver disease, excluding hepatic encephalopathy caused by acute liver disease.*	In line with the licence for rifaximin α, the manufacturer considered adult patients with recurrent episodes of hepatic encephalopathy caused by chronic liver disease (cirrhosis). The rifaximin α licence is for the reduction in recurrence of episodes of overt hepatic encephalopathy in patient's ≥18 years of age (rifaximin-α, summary of product characteristics 2013). Cirrhosis, the chronic liver disease in question, is characterised by episodes of decompensation (acute **on** chronic liver disease). Rifaximin-α is for the prevention of decompensation episodes characterised by the presence of HE. It is not for the treatment of acute HE episodes. Other causes of acute hepatic failure that do not subsequently develop a chronic phase would not be amenable to rifaximin-α therapy, as there would be no future expected episodes of HE to prevent. By definition, hepatic encephalopathy caused by acute liver disease, is acute and unlikely to recur, therefore rifaximin-α is not licensed for these patients. In addition, none of the patients studied with rifaximin-α in the RFHE3001 / RFHE3002 trial populations or the regulatory submission had acute liver disease. All evidence to support the submission to NICE is based on patients with chronic not acute liver disease and we are not of aware of any clinical data with rifaximin-α 550mg to support its use in acute liver disease.
10.			*Patients with more severe liver disease (MELD score of 25 or more) were excluded from the analysis*	For clarity, patients with MELD score ≥25 were excluded from RFHE3001 for a number of reasons, including the ethical and practical constraints of assessing and studying patients with severe liver disease who are often close to the end of their life.
11.	Cost-effectiveness evidence: 3.30	20 - 21	*However, the ERG noted the manufacturer's assertion that the results would apply to this population as well. The ERG was concerned about the validity of this assumption, given that the treatment effect of rifaximin α compared with placebo was not statistically significant in the subgroup with MELD scores of 19 to 24 (the more severe MELD score category in the trial).*	Norgine would like to clarify that non significance was due to small 'n' numbers of patients (26 out of 299). The data did, however, show a trend towards significance.

12.	Cost-effectiveness evidence: 3.39	26	*i. The ERG noted that although more patients had an episode of hepatic encephalopathy in the placebo arm than in the rifaximin-α arm, the rate of hospital admission for those who had an episode was higher in the rifaximin-α arm.* *ii. Therefore, the overall effect of the costs of hospital admission on the ICER was neutralised to some extent, indicating that this was not a key driver of the cost-effectiveness results.*	(i) Norgine has revisited the model and can confirm that this was an error in the analysis of the data. The model has since been corrected in line with the secondary endpoint of RFHE3001 and shows that the rate of hospitalisations in the rifaximin-α arm was lower than that of the placebo arm. (ii) This clearly has an impact on the validity of the second statement.
13.	Consideration of the evidence: 4.1	27-28	*It heard that rifaximin-α was the only licensed treatment available to maintain remission from hepatic encephalopathy episodes.*	Please see below for the exact licence rifaximin-α: Rifaximin-α is licensed for the reduction in recurrence of episodes of overt hepatic encephalopathy in patient's ≥18 years of age (Rifaximin-α, Summary of Product Characteristics 2013)
14.	Clinical effectiveness 4.2	29	*The clinical specialists stated that rifaximin-α would not generally be prescribed for these patients because it was unlikely to provide any meaningful benefit.*	It is Norgine's understanding, based on recent discussions with clinical experts, that whilst rifaximin-α may not be generally prescribed for these patients due to the likelihood of limited clinical benefit, patient would nonetheless benefit from QoL improvements.
15.	Clinical effectiveness 4.7	33	*The manufacturer stated that the patients who had an overt episode had to discontinue the study and were hospitalised, and their recall was not very good.*	This statement is factually incorrect as patients who had overt episodes of hepatic encephalopathy within the RFHE3001 were not necessarily hospitalised. However, all patients who had a breakthrough episode of HE or an HE related hospitalisation were discontinued from the study (please see Section 9, page 33 of the CSR for RFHE3001)
16.			*In particular, 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*	The Time Trade Off (TTO) and Standard Gamble utility studies were conducted in line with standard methodology. Moreover, it is normal practise to include probability of mortality as part of the methodology.
17.			*It also considered that the final utility estimates used in the model were too high, especially for people with underlying liver disease. The Committee concluded that it would be more appropriate to incorporate the quality of life data collected from RFHE3001 in the model and any external data should only be used to supplement and validate this.*	Norgine believe, via consultation with clinical experts that the current economic model has not captured the disutility from episodes of HE and the associated consequences for resource use. Norgine is now carrying out further analyses which may address these issues.