Norgine Clarification on Factual Inaccuracies in the ACD on Rifaximin-α 550mg issued Nov 2013

Page No	Section of ACD	Relevant Text	Norgine Clarification
Page 12-13	ACD Section 3.14	In the original submission, a Markov cohort model consisting of 3 states (remission, overt and dead) was developed to reflect the clinical pathway of hepatic encephalopathy.	The model in the original submission always had two phases held within its structure. An initial phase describing patients moving from an covert C_1 state to an Overt O_1 state and then subsequently a second phase of patients that experience a second covert state C_2 and a subsequent second Overt event. Norgine accept that it was not well described in the first submission. The secretariat indicated that there should not be substantial structural change to the model presented at the second stage of the process. Norgine thus did not modify this two phase structure in its second submission. The company did change the data inputs and mathematical extrapolations to better fit clinical expert opinion and feedback from the appraisal committee.
	Section 3.19 Page 16	The manufacturer used the aggregated 6-month probability rather than individual probabilities of 61.29% for rifaximin-α and 49.32% for placebo on the basis that <u>the rates of hepatic encephalopathy hospital admissions in the trial were not statistically significantly different between the 2 arms.</u>	Use of the word 'rates' is incorrect in this context. Rifaximin-α 550mg reduces the rate of hospitalisation due to HE compared to placebo. This was demonstrated clearly as a secondary endpoint of the pivotal study RFHE3001. Fewer patients in the rifaximin-α group (19/140) were hospitalised than the placebo group (36/159) - hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P = 0.01).
	Section 3.19 Page 16	However, in the revised analysis, the manufacturer applied the aggregated 6-month probability of 52.88% to both arms of the model. <u>The manufacturer used the aggregated 6-month probability rather than individual probabilities of 61.29% for rifaximin-α and 49.32% for placebo on the basis that the rates of hepatic encephalopathy hospital admissions in the trial were not statistically significantly different between the 2 arms.</u>	In line with the statement above, the probability of a patient who had experienced an episode of being hospitalised was not statistically significantly different between study arms (of 61.29% for rifaximin-αand 49.32% for placebo p=0.263). Hence the use of aggregated probability (52.88%).
Page 18	Section 3.21	No administration costs were included in the model because rifaximin-α and lactulose are taken orally; therefore the total costs of treatment per	Comment – are these costs correct for the overt state? All other comments are on pdf Descriptive of: • Covert health state cost: applicable equally to

		month were £288.34 for the rifaximin-α group compared with £7.31 for the placebo group. The manufacturer estimated a total monthly cost of £36.89 for an outpatient visit in the remission state and £359.73 compared with £292.96 for the overt state (outpatient visit plus hospital admission for 5 days) for the rifaximin-α and placebo groups respectively.	both arms – £58.76 monthly (quarterly Hepatology outpatient attendance) • Overt Health state cost: applicable equally to both arms - £1040.77 ([5 days inpatient hepatology admission x 52% risk hospitalisation] + outpatient attendance. • Drug cost: rifaximin - £289.95 monthly (£281.80 rifaximin, £8.15 lactulose); standard of care - £9.09 monthly (lactulose) The original model had incorrectly specified the Hepatology outpatient attendance tariff (resulting in an underestimate).
Page 27	ACD Section 4.2	However, the Committee noted that mortality was not reported because the data were not considered mature enough to assess mortality.	Mortality was reported in RFHE3001 but as the study was of only 6 months duration the data were not considered mature enough to inform the economic model.
Page 28	Section 4.3 (Summary of Appraisal Committee's key conclusions Page 40 - 45)	However, the improvements in asterixis score and venous ammonia levels were not statistically significant, and the difference in changes in CLDQ fatigue scores, SF-36 scores and Epworth Sleepiness scale scores between the rifaximin-α arm and placebo arm was minimal	To clarify, these were tertiary endpoints (ESS and SF36) for which the trial was never powered. Also, patients who had an episode of BOHE exited the trial (RFHE3001) as per the study protocol. Therefore, patients for whom QoL data were available at end of study were all in the covert (minimal HE) state as they were at the beginning of the study. Consequently, it cannot be expected (a priori) that statistically significant unadjusted differences in QoL would be detectable between baseline and last measurement. It is important to note that, because of altered mental and neuromotor status, it was not possible for subjects to complete the CLDQ, SF-36 and other QoL assessments during an overt HE breakthrough episode. Measurements would have been made after recovery from the overt episode. Therefore, as mental status was closer to baseline levels at the time of end of treatment assessments, QoL results may have been similar to baseline levels for subjects who had breakthrough overt HE episodes The planned statistical analysis did not take into account that patients at the end of the study would be those who never experienced a BOHE and was flawed in that respect. Post hoc analysis of CLDQ data (Sanyal et al 2011) showed significant improvement for rifaximin over placebo in all domains of disease-specific QoL and in 27 of 29 individual item responses.

			As we have previously stated, QoL is extremely difficult to measure in these patients. For the following reasons: 1. Cognitive impairment whereas patients believe they are perfectly normal 2. Generic measures e.g. SF36 3. Time weighted averages are the most useful way of capturing **Reference:** Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. Alimentary Pharmacology & Therapeutics 2011; 34: 853–61.