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Dear [redacted],

Re: Single Technology Appraisal – Rifaximin for maintaining remission from episodes of hepatic encephalopathy

The Evidence Review Group (Peninsula Technology Assessment Group) and the technical team at NICE have now had an opportunity to take a look at submission received on 15th February by Norgine Pharmaceuticals Ltd. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 26 March 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Nwamaka Umeweni – Technical Lead (Nwamaka.umeweni@nice.org.uk)

Any procedural questions should be addressed to Kate Moore – Project Manager (Kate.Moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Statement of the decision problem (Section 5 of STA submission)

A1. **Priority Question:** The base case analysis in the submission is based on a comparison of rifaximin with placebo (with both treatment groups receiving concomitant lactulose as per the clinical trial). However, the comparators defined by NICE in the final scope are lactulose, neomycin and neomycin with lactulose.

- Please provide further justification why you have chosen to compare rifaximin with placebo (with concomitant lactulose in both arms) in the base case rather than the listed comparators.
- The ERG has identified a 6 month trial of rifaximin compared with neomycin which could be relevant to the appraisal (Miglio F et al Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. Current medical research and opinion 1997;13(10):539-601. Please reconsider including neomycin as a comparator or alternatively, present any justification for excluding it in the light of this study.

Section B: Clarification on effectiveness data (Section 6 of STA submission)

B1. For trial RFHE3001, to complete the information on randomisation and blinding, please provide a description of the placebo and indicate if it was tested that the intervention was indistinguishable from the placebo.

B2. In trial RFHE3001, please explain the difference in the numbers in the intervention (140) and control (159) arms given the 1:1 randomisation schedule.

B3. **Priority Question:** For trial RFHE3002, please provide the Kaplan-Meier curves to first episode between those “new to rifaximin” and “continuing rifaximin” separately, instead of together as provided in the submission.

B4. In trial RFHE3001, patients were excluded once the first episode of hepatic encephalopathy had occurred. However, the submission states that some of these patients were eligible to join trial RFHE3002. Therefore could you please provide:

- The number of people who joined trial RFHE3002 under “continuing rifaximin” who were excluded from trial RFHE3001 due to experiencing a first episode. That is, how many of the 70 patients in the second trial (RFHE3002) had experienced an episode of hepatic encephalopathy with rifaximin within the first trial (RFHE3001).
- **Priority Question:** For these patients, at what point did their first episode occur in the first trial (RFHE3001) and if there was an episode for these patients in the second trial (RFHE3002) at what point did this occur?

B5. For trial RFH3002, it is stated that patients can continue on treatment even if an episode of hepatic encephalopathy occurs. Can you please provide data on:

- The number of individuals who continued on treatment despite an episode of hepatic encephalopathy.
- **Priority Question:** For these patients, at what time point did the first episode occur and at what time did any subsequent episodes occur?

Section C: Clarification on cost-effectiveness data (Section 7 of STA submission)

C1. Please explain why the identified economic study Huang et al (2007), on page 92 of the submission, was not considered to be relevant and consequently excluded.

C2. Page 97 of the submission currently states that a five-year time horizon adequately captures the health benefits and costs relevant to this appraisal. Please provide additional justification for this and also explain any other reasoning for why a 5 year time horizon for the economic analyses was considered appropriate.

C3. **Priority Question:** As stated on page 98, the recommended dose for lactulose is 30 – 50ml 3 times daily (90ml-150ml per day). However, in the RFHE3001 study the mean dose of lactulose taken by patients was 3.14 – 3.51 cups per day which is equivalent to 47ml – 53ml per day based on the conversion metric provided. Please explain why the dose of lactulose taken by patients in the trial is less than the recommend dose.

C4. **Priority Question:** It is noted that a Lognormal distribution was used to fit the combined dataset (RFHE3001 and RFHE3002) and to extrapolate the study results beyond six months.

- Please justify the choice of the Lognormal distribution.
- More specifically, please provide Log-cumulative hazard plots to assess the underlying accelerated failure time assumption in the Lognormal distribution.
- It is understood that the combined trial data were fitted to the Exponential, Weibull, Gompertz, Lognormal and Logistic distributions. For sake of completeness, please provide a scenario where the Gamma distribution is used to fit the data and the respective coefficients or provide the rationale for excluding its use. We also ask that you justify the choice of the distributions tested in the sensitivity analysis (page 133).

C5. **Priority Question:** For Table 38 (page 117), could you please explain:

- Why Conn score 1 is considered to be an overt episode and included in the weighted QALY estimate?
- Why the percentage of patients with a hepatic encephalopathy episode does not add to 100%?

C6. **Priority Question:** Could you please confirm and clarify the calculations in Table 39 (page 117). Values reported as daily seem to be monthly, and we have not been able to replicate your calculations.

C7. **Priority Question:** The base-case results (table 50, page 128) have not been presented in the required format. Please refer to the STA submission template (table B24, page 53) for the preferred format of presenting the base-case results which should include the incremental results. Please present the results accordingly.

Section D: Textual clarifications and additional points (Appendices)

D1. **Priority Question:** Appendix 2: Effectiveness search

- Please clarify why the Medline/Cochrane search was not updated for the submission.

- Please clarify why the Embase and Econlit searches were only run to 2010.

D2. **Priority Question:** Appendix 8: Adverse effects

- Please clarify why separate searches for adverse events literature were not undertaken outside of the methodologically limited effectiveness and cost-effectiveness searches.

D3. **Priority Question:** Appendix 10: Cost-effectiveness search

- Please clarify why the search was not updated for the submission.

D4. **Priority Question:** Appendix 12: Measurement and valuation of health effects

- Please clarify why the search was not updated for the submission.
- Please clarify why this search was only updated in PubMed.