13/04/12

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Dear Roben,

Re: Single Technology Appraisal – Alteplase for the treatment of acute ischaemic stroke [review of TA122]

The Evidence Review Group (ScHARR Technology Assessment Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on 23 March, 2012 from Boehringer Ingelheim. 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, Friday 27th April, 2012**. 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 Matthew Dyer – Technical Lead (matthew.dyer@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell – Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Dr Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority Request.** With reference to the QUOROM diagram on page 39, please provide a list of the 58 studies excluded after being retrieved for more detailed evaluation, providing the reason for exclusion for each individual study. In particular, please list the 8 studies excluded due to having a "non UK population" and explain specifically why these studies are not relevant.

A2. Health-related quality of life is included as an outcome in the decision problem (Table 6 on page 26), but no data is provided on this outcome from the any of the included trials. Please confirm whether any of the included studies provide a direct comparison of health related quality of life in patients treated with alteplase compared with placebo and present any data available.

Section B: Clarification on cost-effectiveness data

A3. **Priority Request.** The economic model provided to the ERG replicates the results in Table 39 on page 111, i.e. the base case scenario for treatment within the 0 to 4.5 hr timeframe. Please provide two further copies of the economic model with parameter inputs appropriate for each of the time frames; 0-3hrs and 3-4.5hrs, which replicate the results in Tables 45 and 47 (pages 119 and 120) and which include the correct parameters for the probabilistic sensitivity analysis to allow the ERG to replicate the simulations used to produce figures 8, 9, 10, 12, and 13 and to populate Tables 44 and 51.

A4. **Priority Request.** In the economic model, the results table shown in cells B24:J29 of the sheet named "Results" appears to use only the first 50 Monte Carlo simulations to calculate summary statistics for the probabilistic sensitivity analysis. Please confirm whether the data in Tables 44 and 51 on pages 115 and 124 of the manufacturer's submission are based on the full 10,000 simulations and if not, please provide revised tables which are based on the full simulation results. Please provide summary cost-effectiveness results of the format given in Tables 44 and 51 for treatment within 0 to 3hrs.

A5. **Priority Request.** Please provide a) deterministic sensitivity analyses of the form shown in Table 40 and Figure 7 (pages 112-113) for treatment within 0 to 3hrs; b) summary cost-effectiveness results of the format given in Tables 44 and 51 for treatment within 0 to 3hrs and; c) a scatter plot similar to that shown in Figure 8 on page 116 for treatment within 0 to 3hrs.

A6. Section 6.7.1 states that the health state distribution has been reset to use the ECASS III study. Please confirm whether this is only for the purpose of generating the data in Table 33 on page 105 and whether the Lothian Stroke Registry has been used to provide the health state distribution in the standard care arm for the base case analysis.

A7. Please clarify why the rate of symptomatic intracranial haemorrhages (sICH) in the standard care arm has been taken from ECASS III and why it is "problematic" to use rates from the studies described in Table 21 on page 83 for each of the scenarios listed in Table 21.

A8. Table A26 on page 297 shows the absolute risk of sICH used in the model for each scenario. Please provide a table showing the actual absolute risk of sICH from the relevant trials for each scenario alongside the risks used in the model.

A9. Please provide univariate sensitivity analyses for the base case scenario in each time window (0 to 3hrs, 3 to 4.5hrs and 0 to 4.5hrs) applying the actual rates of sICH from the relevant trial populations (i.e. those used to provide the efficacy evidence)

A10. The data in Tables 30 and 31, suggest that the sICH risk for the alteplase arm (2.39%) has been taken from the ECASS III study whereas Table 21 and Table A26 would suggest a lower rate (1.05%) is applicable in the 0 to 4.5 hr treatment window. Please confirm which rate has been applied in the base case analysis for the 0 to 4.5 hr treatment window for both the deterministic and probabilistic analysis.