National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Alteplase for the treatment of acute ischaemic stroke (review of TA 122)

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from the School of Health and Related Research (ScHARR), The University of Sheffield, to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, **14 June 2012** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2. Second paragraph. It is stated that in the ECASS III trial, death or dependency at three months follow up did not show statistically significant treatment effect. This is misleading because as indicated in the clinical effectiveness section of the ERG report (p23), using the definition of death or dependency which was the primary outcome of this study, treatment effect did show statistical significance.	We would suggest that the wording from paragraph 2 of page 2 is removed: **For the 3-4.5 hour treatment window, the main evidence used in the MS is the ECASS III** **RCT. This RCT included n=418 alteplase and n=403 placebo participants. In the ECASS III trial, death or dependency at three months follow-up did not show a statistically significant** **treatment effect, RR 0.87 (95%CI 0.73-1.05) p=0.14, although the midpoint favoured alteplase.** It should be replaced with the following (slightly amended) wording from page 23: **For the ECASS III RCT, the primary outcome was mRS 0-1.** **At three months follow-up, 52.4% (n=219) of the group assigned to alteplase treatment had an mRS score of 0 or 1, significantly (p=0.04) more than for the placebo group (45.2%,** **n=182).** **For the definition of death or dependency (mRS 3-6) (used in the health economic model), ECASS III at three months follow-up 33.5% (n=219) of the group assigned to alteplase treatment, and 38.5% (n=155) of**	It is important in the summary of the clinical effectiveness evidence submitted by the manufacturer that the only reference to the effectiveness outcomes from the pivotal study for alteplase use in the 3-4.5 hour window (ECASS III) should not be solely limited to an outcome that was not statistically significant without making reference to the primary outcome of the study which was statistically significant. Presently, the summary gives a misleading impression of the clinical data as it relates to ECASS III.	This is not a matter of factual accuracy. The clinical outcomes summarised in the executive summary of the ERG report are only those which have a direct impact on the cost-effectiveness estimates. One of these outcomes is the composite outcome of death or dependency, in which dependency is defined as an mRS≥3. It is commented that this outcome is also specified as the primary outcome for the review of effectiveness data conducted by the manufacturer (Tables 7 and 8 of the MS). Results for the primary outcome of the ECASS III trial, which used an alternative definition of dependency (mRS≥2), are provided on page 23 of the ERG report. The MS does not provide a meta-analysis of the death or dependency outcome when using this definition of dependency (mRS≥2) for the other relevant trials. This is

	the group assigned to placebo treatment were either dead or dependent. This did not differ significantly between treatment groups RR 0.87 (95%CI 0.73-1.05).		consistent with it not being the primary outcome for their effectiveness review. The ERG considers that it would be inappropriate to include a description of this outcome in the executive summary for the ECASS III trial without also providing equivalent data for the 0 to 3 hours population, which are not available.