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Alteplase for the treatment of acute ischaemic stroke: A NICE Single Technology Appraisal; an Evidence Review Group perspective.

Short header: Alteplase for acute ischaemic stroke.

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Abstract

Background: The National Institute for Health and Care Excellence (NICE) invited Boehringer Ingelheim GmbH, the manufacturer of alteplase, to submit evidence for the clinical and cost-effectiveness of alteplase for the prevention of strokes as part of NICE's single technology appraisal (STA) process. The comparator was standard medical and supportive management that does not include alteplase, as identified in the scope issued by NICE. The School of Health and Related Research at the University of Sheffield were commissioned to act as the Evidence Review Group (ERG). This paper provides a description of the company submission, the ERG review and NICE's subsequent decisions.

Objective: To critique independently the evidence submitted for consideration by the NICE Appraisal Committee (AC).

Methods: The ERG produced a critical review of the evidence for the clinical and cost effectiveness of the technology based upon the manufacturers' submission (MS) to NICE.

Results: Clinical effectiveness evidence for alteplase was derived from 5 trials. Estimates of clinical effectiveness were provided in the submission for three treatment windows: 0-4.5 hours, 0-3 hours and 3-4.5 hours from symptom onset. For the 0-3 hour treatment window, no additional trials were identified to those included in the original STA (TA 122). The ECASS III randomised controlled trial (RCT) provided the main evidence for the 3-4.5 hour treatment window. In this trial, death or dependency at three months follow-up did not show a statistically significant treatment effect, although the midpoint favoured alteplase. In terms of safety, there was no statistically significant difference in all cause mortality at 3 months, but there was a significantly increased risk of symptomatic intracranial haemorrhage (SICH). Evidence for the 0-4.5 hour treatment window was obtained from a meta-analysis of 3 trials which indicated that the reduction of death and dependency, due to alteplase, was statistically significant, however there was also a significant increase in SICH. The economic model described in the MS was considered by the ERG to meet the NICE reference case. The model structure was considered to be appropriate and the ERG has no major concerns regarding the selection of data used within the model. The incremental cost-effectiveness ratios for the 0-3, 3-4.5 and 0-4.5 hour treatment windows were all well below accepted willingness to pay thresholds.

Conclusion: The ERG had no major concerns regarding the completeness of the submission or the robustness of the evidence presented. The RCTs included were generally of good quality. The main area of uncertainty with regard to clinical effectiveness related to differences in stroke severity at baseline, which potentially favoured alteplase, in two of the three key trials.

In the cost-effectiveness analysis the main driver of decision uncertainty was the lack of precision around the efficacy estimates. However, for all of the treatment windows considered, alteplase was found to be cost-effective compared with standard treatment.

Key points for decision makers

- Alteplase administered between 0 and 4.5 hours after onset of stroke symptoms was considered to be an effective treatment for acute ischaemic stroke because it decreased the probability of death or dependence.

- A significantly higher proportion of patients in the alteplase arm had symptomatic intracranial haemorrhage within 10 days compared with the placebo arm for the 0 to 4.5 hour treatment window.

- The balance of risks and benefits may be slightly different depending on whether alteplase is administered within 0 to 3 hours or within 3 to 4.5 hours of symptom onset.

- Alteplase either dominated standard care or had an incremental cost-effectiveness ratio (ICER) below £10,000 per quality adjusted life years (QALY) gained depending on the time-to-treatment window considered.

- Extension of the time window for treatment should not diminish the urgency with which people suspected of having an acute ischaemic stroke should be treated.

1. Introduction

Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources to be recommended for use within the NHS in England and Wales. The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. The NICE single technology appraisal (STA) process usually covers new technologies soon after the UK market authorisation and is specifically designed for the appraisal of a single health technology, within a single indication [1].

Within the STA process, the manufacturers provide NICE with a written submission, alongside a mathematical model that summarises the manufacturer's estimates of the clinical and cost effectiveness of the technology. This submission is reviewed by an external academic organisation independent of NICE [the Evidence Review Group (ERG)], which consults with clinical specialists, and an ERG report is produced. After consideration of the manufacturers' submission, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee usually formulates the preliminary guidance, the Appraisal Consultation Document (ACD), which indicates the initial decision of the Appraisal Committee regarding the recommendation (or not) of the intervention.

Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a subsequent ACD may be produced or a Final Appraisal Determination (FAD) is issued, which is open to appeal. An ACD is not produced when the intervention is recommended without restriction; in this instance, a FAD is directly produced.

In June 2007 NICE issued guidance recommending alteplase for the treatment of acute ischaemic stroke (AIS) within 3 hours of the onset of stroke symptoms.[2] On 14 March 2012 the manufacturer received approval from the Medicines and Healthcare products Regulatory Agency (MHRA) extending the use of alteplase to within 4.5 hours of the onset of symptoms. The previous NICE guidance has therefore been reviewed to include treatment with alteplase up to a 4.5 hour window and this paper presents a summary of that review. Full details of all the relevant appraisal documents (including the appraisal scope, ERG report, manufacturers and consultee submissions, FAD, and comments on each of these) can be found on the NICE website at:http://guidance.nice.org.uk/TA264.

2. The clinical condition and background

Stroke is a serious medical condition in which the blood supply to the brain is disrupted, potentially resulting in disability and mortality. The World Health Organisation (WHO) defined stroke as rapidly developing clinical signs of focal (sometimes global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin [3]. Symptoms of stroke include numbness, disrupted vision, slurred speech, confusion and headache. There are two major types of stroke: ischaemic stroke

which accounts for 85% of strokes, and is caused by a disrupted blood supply due to narrowing or blockage of the circulatory system; and haemorrhagic stroke which accounts for about 15% of strokes and is due to blood loss in the brain from arteriolar hypertensive disease resulting in neurological damage. It is often difficult for clinicians to identify the particular stroke subtype without access to evidence from an autopsy or brain scan, and therefore a large number of deaths are recorded as either 'unspecified stroke' or 'other cardiovascular disease' [4].

Stroke is the second largest cause of death in the United Kingdom after heart disease [5]. Over 56,000 deaths due to stroke were recorded in England and Wales in 1999, which represents 11% of all deaths recorded that year [6]. Annually about 110,000 people in England have a first or recurrent stroke, [7] and a further 54 000 individuals have a transient ischaemic attack (TIA) in England each year [8].

More than 900,000 people in England are living with the effects of stroke, with half of these being dependent on other people for help with everyday activities [8]. Stroke causes a greater range of disabilities than any other condition, [9]and causes secondary medical problems, including dementia, depression, epilepsy, falls and fractures which place a considerable burden on the economy in England, resulting in an estimated annual direct cost to the National Health Service of £2.8 billion in 2001 [6].

3. The technology

Alteplase (Actilyse, Boehringer Ingelheim) is a tissue plasminogen activator manufactured by recombinant DNA technology. It activates the production of plasmin from its precursor plasminogen. Plasmin is an enzyme which degrades fibrin clots. The aim of treatment is to reduce the impact of ischaemia by restoring blood flow through the occluded (or blocked) artery. It is administered by intravenous infusion.

A UK licence for the use of alteplase within a 0-3 hour administration time period from the onset of symptoms for the treatment of AIS was granted in September 2002. The manufacturers received licence approval from the MHRA for alteplase use to be extended to 4.5 hours from the onset of symptoms on 14th March 2012.

The cost of alteplase was £135 per 10-mg pack, £180 per 20-mg pack and £300 per 50-mg pack (excluding VAT; 'British national formulary' [BNF] edition 63) at the time of appraisal by NICE [10]. The cost per course of treatment depends on the body weight of the patient, and can range from £300 to £600 based on a recommended dose of 0.9 mg per kilogram of body weight. Costs may vary in different settings because of negotiated procurement discounts.

As the use of alteplase is solely additive and not intended to replace any routine practice the correct comparator is placebo or standard medical and supportive management without thrombolysis. This is appropriate given that no thrombolytic treatment other than alteplase is licensed in the UK for this purpose. As the most important therapy in AIS is restoration of the

blood supply to the affected area of the brain [11], other stroke treatment or prevention therapies, which function in different ways, would not be relevant comparators.

Alteplase should only be administered after exclusion of intracranial haemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive for the presence of haemorrhage.

The most common complication during alteplase therapy is bleeding. Should serious bleeding occur in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial), alteplase therapy should be discontinued immediately, along with any concomitant therapy with heparin.

4. The independent ERG review

The manufacturer provided a submission to NICE on the use of alteplase within its licensed indication for the treatment of acute ischaemic stroke. The comparator was standard medical and supportive management that does not include alteplase as identified in the scope [12] issued by NICE. The ERG report comprised a critical review of the evidence for the clinical and cost effectiveness of the technology based upon the manufacturer's submission (MS) to NICE. The review embodied three aims:

- To assess whether the MS conformed to the methodological guidelines issued by NICE;
- To assess whether the manufacturer's interpretation and analysis of the evidence was appropriate;
- To indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help to inform NICE guidance.

The ERG conducted a detailed critical appraisal of the MS. As part of this process the ERG had the opportunity to obtain clarification on specific points in the MS. The ERG were satisfied with the responses received from the manufacturer which included revised models, submitted after the ERG identified a summation error in the results sheet of the original model, and some additional sensitivity analyses.

4.1. Clinical evidence

The MS identified 10 randomised controlled trials of alteplase in AIS, of which five provided relevant data and were included in either the main analyses or the sensitivity analyses [13–18]. The time-frame for onset to treatment varied across the trials with no single trial providing a randomised comparison of treatment within 0 to 4.5 hours of symptom onset. Estimates of clinical effectiveness were provided in the submission for three treatment windows: 0 to 4.5

hours, 0 to 3 hours and 3 to 4.5 hours from symptom onset. This subgroup analysis examining symptom onset to treatment time was pre-specified in the scope.

The main outcomes addressed in detail within the submission were death, death or dependency and symptomatic intracranial haemorrhage (SICH). Dependency was defined as a score of 3 to 5 on the Modified Rankin Scale (mRS). The composite outcome of death or dependency is assumed to capture both the treatment effect of alteplase and the adverse impact of any treatment related SICH.

For the 0-3 hour treatment window, there were no additional trials identified to those included in the 2007 NICE STA of alteplase for the treatment of acute ischaemic stroke (TA122) [2]. The main trials providing evidence for the 0 to 3 hour treatment window were the NINDS trial [13], which examined treatment within 3 hours and the ECASS II trial [14], which stratified randomisation by onset to treatment time providing a pre-specified subgroup analysis for patients treated within 3 hours. The inclusion of further evidence from the ATLANTIS trials [15, 16] (which did not stratify randomisation by 0-3 hours) was explored in a sensitivity analysis although these estimates were informed by an ad-hoc subgroup analysis. Death or dependency at three months follow-up significantly favoured alteplase, relative risk (RR) 0.81 (95%CI 0.72-0.92) p=0.002, by random-effects meta-analysis of the two main trials which included 393 participants allocated to alteplase, and 389 to placebo. In terms of safety, there was no statistically significant difference in all cause mortality at 3 months in either the fixed or random effects meta-analysis. There was a significantly increased risk of SICH, RR 4.90 (95%CI 1.90-12.61) p=0.001, by fixed effects meta-analysis, but the difference was not statistically significant by random effects meta-analysis, RR 3.94 (95%CI 0.61-25.47) p=0.15. The results of the sensitivity analysis incorporating data from the ATLANTIS trials [15, 16] were similar, although in this analysis the RR for SICH was significantly higher for both the fixed and random effects meta-analysis.

For the 3-4.5 hour treatment window, the main evidence used in the MS was the ECASS III RCT [17, 18]. This RCT included 418 alteplase and 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. In terms of safety, there was no statistically significant difference in all cause mortality at 3 months, but there was a significantly increased risk of SICH, RR 4.82 (95%CI 1.06-21.87) p=0.04. The inclusion of further evidence from the ECASS II [14] and ATLANTIS trials [15, 16] (which did not stratify randomisation according to treatment within 3-4.5hours of symptom onset)was explored in a sensitivity analysis, although this relied on ad-hoc subgroup analyses from these trials.

Considering the 0-4.5 hour treatment window, random-effects meta-analysis of the two main trials of 0-3 hours, (n=393 alteplase and n=389 placebo), and the main trial of 3-4.5 hours, (n=418 alteplase and n=403 placebo), showed a RR for death or dependency of 0.83 (95%CI

0.75-0.92) p=0.0006, significantly favouring alteplase. Again, there was no statistically significant increase in all cause mortality at 3 months, but there was a significantly increased risk of SICH. Heterogeneity between the three studies was low (I^2< 25%) for the outcomes of death and death or dependency, but higher for SICH (I^2=42%). However, the heterogeneity across the three studies was lower than that seen when pooling data from the two trials examining 0-3 hours, as the results of the ECASS III study [17] were closer to those of the large NINDS study [13] than the small subgroup analysis of the ECASS II study [14].

4.1.1. Critique of clinical evidence and interpretation

The ERG believes that all relevant RCTs were identified in the MS. The evidence submitted in the MS reflected the decision problem within the NICE final scope with all included trials providing relevant data. The analyses presented were restricted to participants for whom alteplase was administered within 4.5 hours of symptom onset, and so this accurately reflected the NICE scope. The RCTs included were generally of good quality with regard to randomisation and having blinded outcome assessors. However, both the NINDS, one of the two main trials for 0-3 hours, and the trial contributing most participants for 0-3 hours, and the ECASS III RCT, providing the main evidence for 3-4.5 hours, had imbalances in baseline stroke severity favouring alteplase. There is disagreement in the literature as to whether the imbalance in the NINDS trial would significantly skew treatment effect outcomes [19,20]. All of the RCTs used appropriate statistical techniques and conducted an intention-to-treat analysis. The meta-analysis approach was appropriate and both fixed and random effects analyses were provided. The ERG would agree with the exclusion of data derived from ad-hoc subgroup analyses from the base-case meta-analyses. With regard to the pooling of data across different treatment windows, a pooled analysis [21] of 3670 patients from 8 RCTs, which examined the interaction between treatment effect and onset to treatment time, found that there was a significant interaction for the outcomes of death and dependency (mRS of greater than 1) and mortality, but not for SICH. (It should be noted that not all of the 8 RCTs included in the pooled analysis examined the use of alteplase in line with its UK marketing authorisation.) However, the adjusted odds ratios provided by the pooled analysis [21] supports the meta-analysis of the RCT data presented within the MS, in showing a significant treatment effect for dependency and a non-significant difference in mortality at three months for both the 0 to 3 and 3 to 4.5 hour onset to treatment windows.

4.2. Cost-effectiveness evidence

The economic model submitted was an updated version of a published Health Technology Appraisal (HTA) which also formed the basis of Boehringer Ingelheim's submission to TA122 [2]. The model compared treatment with alteplase alongside standard care against a comparator of standard care alone. Estimates of cost-effectiveness were provided for three treatment windows: 0 to 4.5 hours, 0 to 3 hours and 3 to 4.5 hours from symptom onset. The

models for these three treatment windows used different estimates of treatment effect but were otherwise equivalent.

The efficacy estimates used in the basecase scenarios for the three treatment windows were limited to the NINDS (0-3 hours), ECASS II (0-3 hours) and ECASS III (3-4.5 hours) trials as data were available from these trials for the required treatment windows using either the whole trial population or a pre-specified subgroup with randomisation stratified appropriately. Sensitivity analyses were conducted using alternative efficacy estimates which incorporated ad-hoc subgroup analyses of the ATLANTIS trials and ECASS II trials.

Treatment effect was captured by modelling the distribution of patients between the health states dependent, independent and dead at 6 months following treatment. This was based on efficacy outcomes from the trials at 3 months. The only trial providing longer-term follow-up, from a population meeting the licensed indication was NINDS. Results from this trial support the maintenance of benefits from 3 to 6 months and this was considered clinically reasonable. Dependency is defined as a score of 3 to 5 on the mRS. These outcomes were assumed to capture both the impact of alteplase on stroke severity and the impact of any SICH following alteplase. The probabilities of transitions between the health states beyond 6 months were assumed to be equivalent between the two treatment arms and were based on data from the Lothian Stroke Registry (LSR). After the first year, patients remained in the same health state until they either experienced a recurrent stroke or died. Age-specific general population mortality risks were applied after the first year. These were adjusted to account for the higher risk of mortality following stroke. A fixed annual mortality risk was applied after recurrent stroke.

Costs and health-related quality of life estimates applied to the health states were based on published estimates from the UK population [22-24]. The cost of alteplase was dependent on the body weight of the patient. The manufacturer assumed that the mean body weight (76kg) of patients in the SITS-MOST [24] study was representative of the average stroke patient in UK clinical practice. Patients were given 0.9 mg of alteplase per 1 kg of body weight, and so the dose received by a patient weighing 76kg was 68.4mg (76kg * 0.9mg/kg). The cost of 68.4mg alteplase was based on a 50mg pack (£300) plus a 20mg pack (£180) and was thus estimated to be £480. The cost could range from £300 to £600 depending on the individual's weight and the average cost is likely to be higher than £480 as any patient weighing over 78kgs would require two 50mg packs. However, a univariate sensitivity analysis covering this range of cost was presented in the MS. The source of the price of the packs was not referenced in the MS but the prices cited were consistent with those given in the British National Formulary at the time of the appraisal [10].

Estimates of extra staffing requirements associated with administering alteplase were based upon the resource use figures described by Sandercock et al.,[20]. These were considered reasonable by the ERG's clinical advisors. The cost of additional staffing to administer

alteplase, based on the above resource use and costed from the Personal Social Services Research Unit (PSSRU) unit costs [23], was estimated to be £1,316 per patient.

The health related quality of life values used for the dependent and independent stroke states were based on the responses to the EuroQoL quality of life questionnaire of a sample of 147 LSR patients as described in Sandercock et al., [20]. These values were 0.74 (95% CI 0.69-0.79) and 0.38 (95% CI 0.29-0.47) for the independent and dependent stroke states, respectively. It appears reasonable to the ERG that the manufacturer has used the LSR study utilities as these values were elicited from a UK population, and were measured and valued using the EuroQol as per the NICE reference case [25].

Costs and quality adjusted life years (QALYs) were estimated using a life-time horizon with future costs and benefits discounted at 3.5%. The economic perspective was the NHS and the Personal Social Services (PSS). Costs were adjusted to 2012/13 levels using an inflation rate of 3% (based on the Pay & Prices index from PSSRU 2011 [23]).

The impact of parameter uncertainty was estimated in a probabilistic sensitivity analysis. Scenario analyses were run on key parameters.

The ICER (cost per QALY gained) for treatment within 0 to 4.5 hours from symptom onset was estimated at £2,296 when using the mean costs and QALYs from the probabilistic analysis. However, this cost-effectiveness estimate relied on combining efficacy estimates for treatment across two different time windows. When considering treatment within 3 hours, alteplase dominated standard care as the mean QALYs gained are greater and the mean cost is lower than for standard care. However, the ICER for treatment within of 3 to 4.5 hours of symptom onset was less favourable at £6,169 per QALY.

The cost-effectiveness results were generally robust under the sensitivity analyses conducted. The only factor having a significant impact was the lack of precision around the efficacy estimates. The relative risks for the outcomes of death and death or dependency were not statistically significant in the 3 to 4.5 hour onset to treatment window. Applying the upper and lower 95% confidence intervals for both these parameters as point estimates within the model resulted in a large variation in the ICER. The cost-effectiveness estimates for the 0 to 4.5 hour onset to treatment window were similarly sensitive to uncertainty in the efficacy estimates. All of the sensitivity analyses which examined the use of alternative efficacy estimates incorporating ad-hoc subgroup analyses from either the ATLANTIS trials (0 to 3 hour and 3 to 4.5 hour treatment window) or the ECASS II trial (3 to 4.5 hour treatment window) resulted in a decrease in both the QALYs gained and the costs accrued for alteplase compared to the basecase analysis, although none resulted in an ICER greater than £10,000 per QALY.

4.2.1. Critique of cost-effectiveness evidence and interpretation

The economic model described in the MS is considered by the ERG to meet the NICE reference case [25]. The health states included in the model were considered to be appropriate to capture both the treatment effect of alteplase on stroke severity and the impact of SICH following thrombolytic therapy. The evidence used to populate the transition probabilities were considered to be relevant to the UK population. The data from the LRS which are used to determine the health state distribution in the standard care arm are now over 10 years old and may not reflect recent improvements in stroke outcomes following the introduction of specialist stroke units. However, any more recent source is likely to be confounded by improvements resulting from the use of alteplase and would therefore not be a suitable source of natural history data for the standard care arm. The costs and utility values applied to the health states were considered to be appropriate and in-keeping with the reference case. The cost-effectiveness estimates were generally robust under the univariate sensitivity analyses conducted with the main cause of decision uncertainty relating to the precision around the efficacy estimates. The PSA was found to sample independently from the relative risks for death and death or dependency, which ignores the correlation that is likely to exist between these two variables. This may mean that it does not provide an accurate description of the uncertainty around the mean costs and QALYs, although the ERG considers it unlikely that this would have a significant impact on the ICER.

The ERG considers that it was appropriate to conduct separate analyses for the sub-population of patients who are eligible for treatment within 0 to 3 hours and for the sub-population who are eligible for treatment within 3 to 4.5 hours. The efficacy estimates for these two sub-populations suggest that the balance of risks and benefits may be slightly different and these differences in efficacy translate into differing cost-effectiveness estimates, even though the confidence intervals for the efficacy estimates are overlapping and there is no significant heterogeneity between the two treatment windows. Furthermore, neither sub-population has a central ICER estimate above £20,000 per QALY.

The ERG used the submitted models to estimate the global expected value of perfect information (EVPI) for each of the three treatment time windows using a willingness to pay threshold of £20,000 per QALY. The population eligible for treatment over a 5 year period was estimated to be 85,500, 65,400 and 20,100 within 0 to 4, 0 to 3 and 3 to 4.5 hours of symptom onset, respectively. The estimated population global EVPI was £324,000, £6,593,000 and £5,119,000, for treatment within 0 to 4.5, 0 to 3 and 3 to 4.5 hours, respectively. The population global EVPI was estimated to be much higher when considering the 0 to 3 hour and 3 to 4.5 hour time windows separately as there is greater uncertainty in the RRs for death and death or dependency when considering just those studies which are applicable to each sub-population.

5. Conclusions of the ERG report

The ERG had no major concerns regarding the completeness of the submission or the robustness of the evidence presented. The evidence presented in the MS reflects the decision problem identified in the scope. The analyses presented were restricted to participants for whom alteplase was administered within 4.5 hours of symptom onset, and so this accurately reflected the NICE scope [12].

The RCTs included were generally of good quality with regard to randomisation and having blinded outcome assessors. Trial data from ad-hoc subgroup analyses which do not represent a true randomised comparison were excluded from the main results and only considered in sensitivity analyses. The main area of uncertainty with regard to clinical effectiveness related to differences in stroke severity at baseline, which potentially favoured alteplase, in two of the three key trials.

The economic model described in the MS is considered by the ERG to meet the NICE reference case. The model structure was considered to be appropriate and the ERG has no major concerns regarding the selection of data used within the model. In the cost-effectiveness analysis the main driver of decision uncertainty was the lack of precision around the efficacy estimates.

6. Key methodological issues

The main area of uncertainty with regard to clinical effectiveness relates to differences in stroke severity at baseline, which potentially favour alteplase, in two of the three key trials.

In the cost-effectiveness analysis the main driver of decision uncertainty is the lack of precision around the efficacy estimates. The amount of decision uncertainty, represented by the global population EVPI, is dependent on whether one considers the cost-effectiveness of the whole population covered by the licensed indication or whether one looks separately at the subpopulations able to receive alteplase within 0 to 3 hours and 3 to 4.5 hours from symptom onset. Combining data across the two treatment windows increases the precision of the efficacy estimates but also ignores any variation in the balance of risks and benefits that may exist within the licensed population. Alteplase was considered by the appraisal committee to represent an effective use of NHS resources across both subpopulations as it either dominated standard care or had a low ICER compared to standard care depending on the treatment window considered. In this situation, the decision regarding whether to recommend alteplase is not dependent on the committee's judgement regarding the appropriateness of pooling data across the two treatment windows, but the EVPI across the whole licensed population is still dependent on this judgement.

7. NICE guidance

After considering the available evidence from the manufacturer, ERG, expert testimony and other submissions, the NICE appraisal committee issued the following guidance in September 2012:

Alteplase is recommended within its marketing authorisation for treating acute ischaemic stroke in adults if:

- treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and
- intracranial haemorrhage has been excluded by appropriate imaging techniques.

7.1. Consideration of the evidence

The main areas discussed by the Committee and recorded in the Final Appraisal Determination along with the recommendations of the Committee are summarized in the following sections.

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of alteplase, having considered evidence on the nature of acute ischaemic stroke and the value placed on the benefits of alteplase by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

The Committee considered the evidence submitted by the manufacturer on the clinical effectiveness of alteplase. The Committee noted that no clinical-effectiveness data for the 0 to 3-hour treatment window additional to those included in NICE technology appraisal guidance TA122 were available, and that clinical-effectiveness data for the 3 to 4.5-hour treatment window were derived primarily from the ECASS III trial. The Committee considered methodological issues concerning the ECAS III trial and concluded that this trial was of good methodological quality and provided robust evidence of the clinical efficacy of alteplase for the 3 to 4.5-hour treatment window.

The Committee considered the clinical effectiveness of alteplase for the 3 to 4.5-hour treatment window. The Committee concluded that alteplase administered between 3 and 4.5 hours after onset of stroke symptoms was an effective treatment for acute ischaemic stroke because it decreased the probability of disability.

The Committee considered the manufacturer's meta-analyses, which generated alternative estimates of alteplase's effect on all cause mortality and also on death or dependence (mRS score of 3 to 6) at 90 days for each of the 3 treatment windows (0 to 3 hours, 3 to 4.5 hours,

and 0 to 4.5 hours), and which were used for the clinical-effectiveness parameters in the manufacturer's economic model. The Committee noted that the trials included in the meta-analyses for the 0 to 4.5-hour treatment window were of good methodological quality and were sufficiently similar in terms of study design and results. The Committee concluded that alteplase administered between 0 and 4.5 hours after onset of stroke symptoms was an effective treatment for acute ischaemic stroke because it decreased the probability of death or dependence.

The Committee considered the evidence on adverse reactions associated with alteplase. The Committee noted that a significantly higher proportion of patients in the alteplase arm had SICH within 10 days compared with the placebo arm for the 3 to 4.5-hour window in the ECASS III trial and for the 0 to 4.5-hour window in the manufacturer's meta-analyses. However, the Committee noted that while alteplase increased the risk of SICH, the absolute number of patients in the ECASS III trial who had a SICH was small. The Committee heard from the clinical specialists that SICH is the primary cause of death within 7 days for patients receiving alteplase treatment, and that clinicians have difficulty predicting which patients are at high risk. The Committee also noted that the proportion of other reported serious adverse reactions and fatal adverse reactions in the ECASS III trial up to 90 days was similar across the 2 treatment arms. The Committee concluded that, although the increased risk of SICH associated with alteplase is offset by significant improvements in favourable outcomes at 90 days, SICH is an adverse event that needs to be included in modelling of the cost effectiveness of alteplase.

The Committee considered the manufacturer's economic model, the assumptions on which the parameters were based, and the critique and exploratory analyses conducted by the ERG. The Committee noted that the model structure and many of the input parameters were identical to those used in the economic model for NICE technology appraisal guidance TA122 (0 to 3-hour window) and agreed that this approach was appropriate. With regard to the clinical-effectiveness parameters used in the model, the Committee acknowledged that the survival benefit associated with alteplase compared with standard care, which resulted from a point estimate for the relative risk for alteplase treatment and death of less than 1, was appropriately reflected in the economic model. However, the Committee noted that the manufacturer had assumed that the relative treatment effect of alteplase was maintained beyond 90 days up to 6 months in the model with no longer-term survival benefit beyond this point. The Committee considered that this may have been a conservative approach if alteplase offers a survival advantage compared with placebo beyond 6 months, a proposition the Committee found plausible, although not currently proven statistically, given that alteplase was associated with a reduction in death or dependence at 90 days. The Committee was aware that the utility values were not adjusted over time in the model, which may have overestimated the QALYs accrued by people in the independent health state and therefore biased the results in favour of alteplase. However, the Committee considered that this was

not a crucial limitation of the model because the ICERs were not sensitive to changes in the utility values in the manufacturer's sensitivity analyses, and therefore any downward adjustment over time would have had a small impact on the ICERs. The Committee was also aware that the manufacturer assumed that people who had a SICH in the economic model incurred the additional one-off cost of a CT scan but experienced no further disutility beyond that captured in the dependent or independent health states. The Committee heard from the clinical specialists that this assumption was reasonable. Overall, the Committee concluded that the economic model adhered to the NICE reference case for economic analysis and the modelling approach was reasonable.

The Committee considered the most plausible ICERs presented by the manufacturer and also by the ERG in its exploratory analyses. It agreed that alteplase either dominated standard care or had an ICER below £10,000 per QALY gained depending on the time-to-treatment window considered. The Committee noted that none of the additional exploratory analyses undertaken by the ERG resulted in ICERs that varied substantially from those presented in the MS.

The Committee also agreed with the clinical specialists that extending the time window for treatment should not diminish the urgency with which people suspected of having an acute ischaemic stroke should be treated.

The Committee discussed whether any equality issues required consideration in this appraisal. The Committee was aware that extension of the licence to 4.5 hours after symptom onset may enable increased access to treatment with alteplase for patients in remote or rural locations.

8. Conclusion

The Committee concluded that alteplase administered between 3 and 4.5 hours after onset of stroke symptoms was an effective treatment for acute ischaemic stroke because it decreased the probability of disability.

The Committee concluded that alteplase administered between 0 and 4.5 hours after onset of stroke symptoms was an effective treatment for acute ischaemic stroke because it decreased the probability of death or dependence.

The Committee agreed that alteplase either dominated standard care or had an ICER below £10,000 per QALY gained depending on the time-to-treatment window considered. The Committee concluded that treating acute ischaemic stroke with alteplase within 0 to 4.5 hours of onset of stroke symptoms was a cost-effective use of NHS resources.

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Contributions of Authors
MH drafted the final version of the manuscript and takes responsibility as the overall guarantor of the content. SD and ES revised the manuscript for important intellectual content. All authors have given their approval for the final version to be published.

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