

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE**

Final appraisal determination

**Alteplase for treating acute ischaemic
stroke (review of technology appraisal
guidance 122)**

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

This guidance replaces NICE technology appraisal guidance 122 issued in June 2007.

- 1.1 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.

2 The technology

- 2.1 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 that degrades fibrin clots. The aim of treatment is to reduce the impact of ischaemia by restoring blood flow through the occluded (blocked) artery. A UK marketing authorisation for alteplase to treat acute ischaemic stroke within 3 hours of the onset of symptoms was granted in September 2002. On 14 March 2012 the manufacturer received approval from the Medicines and Healthcare products Regulatory Agency extending the use of alteplase to within 4.5 hours of the onset of symptoms. The current marketing authorisation states that treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques.
- 2.2 The summary of product characteristics lists the following adverse reactions for alteplase: haemorrhage (intracranial and gastrointestinal), recurrent ischaemia or angina, hypotension, heart failure, pulmonary oedema and reperfusion arrhythmias. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The cost of alteplase is £135 per 10-mg pack, £180 per 20-mg pack and £300 per 50-mg pack (excluding VAT; 'British national formulary' [BNF] edition 63). 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.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of alteplase and a review of this submission by the Evidence Review Group (ERG; appendix B). The decision problem addressed by the manufacturer considered whether treatment with alteplase was clinically effective compared with standard medical care (standard medical and supportive management that does not include alteplase) for treating acute ischaemic stroke in adults within 4.5 hours of symptom onset, and whether alteplase treatment was a cost-effective use of NHS resources.

- 3.1 The manufacturer carried out a systematic literature search, which was based on a previously published Cochrane review ('Thrombolysis for acute ischaemic stroke'), but restricted the search to randomised controlled trials of alteplase. For the 0 to 3-hour treatment window, the manufacturer identified no trials other than those included in the previous guidance on alteplase in acute ischaemic stroke (NICE technology appraisal guidance 122) from 2007. The trials in technology appraisal guidance 122 included NINDS (National Institute of Neurological Disorders and Stroke) I and II, ATLANTIS ('Thrombolysis for acute noninterventional therapy in ischaemic stroke') A and B, and ECASS (the 'European Cooperative Acute Stroke Study') II. All these trials were multicentre, double-blinded, placebo-controlled randomised controlled trials of alteplase administered at its licensed dose of 0.9 mg/kg. Treatment with alteplase was administered within 3 hours (NINDS I and II), 5 hours (ATLANTIS B) or 6 hours (ATLANTIS A, ECASS II) of onset of stroke symptoms. Patients

were followed up for outcomes for 90 days. The NINDS and ATLANTIS trials were conducted in North America and the ECASS trial in multiple sites in Europe (including the UK), Australia and New Zealand.

- 3.2 The clinical-effectiveness evidence in the manufacturer's submission focused on the extended 3 to 4.5-hour treatment window for which the only directly relevant trial identified by the manufacturer was ECASS III. Other trials with data indirectly relevant to this treatment window were ATLANTIS A and B and ECASS II, from which subgroup data specifically for the 3 to 4.5-hour window were used by the manufacturer in sensitivity analyses. The manufacturer noted that this involved stratifying data into subgroups that had not been specified before randomisation. The manufacturer also identified the 'Third International Stroke Trial' (IST-3), a randomised open-label blinded endpoint trial in which alteplase was administered within 6 hours of symptom onset. However, the manufacturer commented that this trial was not placebo controlled and therefore did not meet its trial selection criteria, and that no published results were available at the time of submission.
- 3.3 ECASS III was a placebo-controlled multicentre trial carried out across 130 sites in 19 European countries. Of the 821 patients 22 were from the UK. Patients were eligible for inclusion if aged between 18 and 80 years, diagnosed with acute ischaemic stroke and able to receive treatment within 3 to 4.5 hours of the onset of stroke symptoms. Before randomisation, brain imaging was used to exclude intracranial haemorrhage. The trial randomly assigned eligible patients to receive 0.9 mg/kg of intravenous alteplase (n=418) or placebo (n=403). Patients were followed up for 90 days for outcomes. Baseline demographic and disease characteristics

were similar between participants in the 2 treatment arms, but the initial severity of the stroke (as assessed by the National Institutes of Health stroke scale [NIHSS; a 15-item quantitative measure of stroke-related neurological impairment]) and the proportion of patients with a history of previous stroke were both significantly higher in the placebo arm.

- 3.4 The primary outcome in ECASS III was the presence or absence of disability at 90 days as assessed by the modified Rankin scale, which measures the degree of disability or dependence in people who have had a stroke and ranges from 0 (symptom free) to 6 (dead). From intention-to-treat analyses, 52.4% of patients randomised to the alteplase treatment arm had a favourable outcome at 90 days (a score of 0 or 1 [no significant disability]) compared with 45.2% of patients randomised to placebo (odds ratio [OR] 1.34, 95% confidence interval [CI] 1.02 to 1.76, $p=0.04$). After adjustment for confounding baseline variables (identified as being statistically significant at $p<0.10$) including treatment arm, NIHSS score, smoking, time from onset of stroke to treatment, and presence or absence of previous hypertension, alteplase remained statistically significantly associated with a favourable outcome (OR 1.42, 95% CI 1.02 to 1.98, $p=0.04$).
- 3.5 ECASS III also reported the composite outcome of death or dependence (defined as a score of 3–6 on the modified Rankin scale) at 90 days. There were no statistically significant differences in the number of patients who were dead or dependent between the alteplase and placebo treatment arms (33.5% compared with 38.5%, relative risk [RR] 0.87, 95% CI 0.73 to 1.05).
- 3.6 The ECASS III trial also reported as a secondary endpoint a global outcome score at 90 days, which combined a score of 0–1 on the modified Rankin scale, a score of 1 on the Glasgow outcome scale

(a 5-point measure of brain injury, with 1 indicating independence and 5 death), a score of 95–100 on the Barthel index (a 10-item measure of a person's daily function, with higher scores reflecting higher function), and a score of 0–1 on the NIHSS. Randomisation to alteplase was associated with a statistically significantly higher probability of achieving a favourable global outcome score (OR 1.28, 95% CI 1.00 to 1.65, $p=0.05$).

- 3.7 The manufacturer presented a summary of adverse reactions based on intention-to-treat analyses in the ECASS III trial at 90 days. Fatal adverse reactions were reported for 7.7% of patients in the alteplase arm and 8.4% of those in the placebo arm. A statistically significantly higher proportion of patients in the alteplase arm had an intracranial haemorrhage (27.0% compared with 17.6%, $p=0.001$) or a symptomatic intracranial haemorrhage (2.4% compared with 0.3%, $p=0.008$) compared with the placebo arm. Three patients (0.7%) randomised to the alteplase arm had a fatal intracranial haemorrhage. Investigator-defined drug-related adverse reactions were reported for 23.9% of patients in the alteplase treatment arm and 6.9% of patients in the placebo arm. Other serious adverse reactions were reported for 25.1% of patients in the alteplase arm and 24.6% of those in the placebo arm.
- 3.8 The manufacturer conducted meta-analyses to calculate the relative risks associated with alteplase for all-cause mortality within 90 days, death or dependence within 90 days, and symptomatic intracranial haemorrhage within 10 days for each of the 3 treatment windows (0 to 3 hours, 3 to 4.5 hours, and 0 to 4.5 hours). The manufacturer presented results from both fixed and random-effects models. For the 0 to 3-hour window, the manufacturer used data from ECASS II and NINDS. and used the relative risks from

ECASS III for the 3 to 4.5-hour window. For the 0 to 4.5-hour window, the manufacturer used data from ECASS II (0 to 3 hours), ECASS III (3 to 4.5 hours) and NINDS (0 to 3 hours). Heterogeneity between the 3 studies was low for the outcomes of all-cause mortality and death or dependence, but moderate for the outcome of symptomatic intracranial haemorrhage.

3.9 The manufacturer compared all-cause mortality at 90 days for the 2 treatment arms. No statistically significant difference was observed between alteplase and placebo for the 3 to 4.5-hour (RR 0.82, 95% CI 0.50 to 1.33, $p=0.42$), the 0 to 3-hour (RR 1.05, 95% CI 0.55 to 2.03, $p=0.88$), or the 0 to 4.5-hour (RR 0.89, 95% CI 0.67 to 1.18, $p=0.41$) treatment windows. For the outcome of death or dependence at 90 days, the manufacturer reported no statistically significant difference between alteplase and placebo for the 3 to 4.5-hour window (RR 0.87, 95% CI 0.73 to 1.05, $p=0.14$). However, a statistically significant difference in favour of alteplase was reported for both the 0 to 3-hour window (RR 0.81, 95% CI 0.72 to 0.92, $p=0.002$) and the 0 to 4.5-hour window (RR 0.83, 95% CI 0.75 to 0.92, $p<0.001$). For the outcome of symptomatic intracranial haemorrhage occurring within 10 days, patients randomised to receive alteplase within the 3 to 4.5-hour window had a statistically significant higher risk (RR 4.82, 95% CI 1.06 to 21.87, $p=0.04$) with similar results for the 0 to 4.5-hour treatment window (RR 4.18, 95% CI 1.39 to 12.53, $p=0.01$). For the 0 to 3-hour window, the manufacturer reported a higher risk of symptomatic intracranial haemorrhage among patients randomised to alteplase that was not statistically significant (RR 3.94, 95% CI 0.61 to 25.47, $p=0.15$).

3.10 The manufacturer conducted a systematic review of published cost-effectiveness analyses but did not identify any studies that

evaluated the cost effectiveness of alteplase for the treatment of acute ischaemic stroke within 3 to 4.5 hours of onset of symptoms. Instead, the manufacturer adapted a published cost-effectiveness analysis (Sandercock et al., 2002) relevant to the decision problem from the previous guidance on alteplase in acute ischaemic stroke (NICE technology appraisal guidance 122) and used this as part of its submission.

- 3.11 The manufacturer developed a Markov model simulating patients with acute ischaemic stroke who do or do not receive alteplase within 4.5 hours of onset of symptoms. Patients were modelled through 3 possible health states: independent, dependent and dead. The independent state was defined by a modified Rankin scale score of 0–2 and the dependent state by a modified Rankin scale score of 3–5. The model had 3 time phases: from 0 to 6 months when the model assumed the treatment effect of alteplase was complete at 90 days and maintained at 6 months; from 6 to 12 months when the model assumed no further treatment effect; and beyond 12 months when the model also assumed no further treatment effect from alteplase. However, beyond 12 months the model assumed that people in the dependent or independent states could have a recurrent stroke. The model also assumed that people in the dependent state at 12 months and beyond do not move to an independent state, and that people in the independent state at 12 months and beyond do not move to a dependent state unless they survive a recurrent stroke. The model assumed a lifetime horizon with a cycle length of 6 months for the first 12 months, followed by cycles of 12 months thereafter.
- 3.12 The manufacturer chose a population for the model based on SITS-MOST ('Safe implementation of thrombolysis in stroke-monitoring study'), a European observational study of patients receiving

alteplase. The manufacturer considered that this study population represented the mean age (68 years) and gender distribution (39.8% female) of patients who would receive alteplase in clinical practice in England and Wales.

- 3.13 For the first phase (0 to 6 months) of the manufacturer's economic model, the size of the effect of treatment with alteplase was informed by the manufacturer's meta-analyses for the 3 treatment windows as described in section 3.8. For the standard treatment arm, the proportion of people in each health state (39.53% independent, 32.56% dependent and 27.91% dead) was informed by the Lothian stroke registry, a registry in Edinburgh, Scotland, of 1779 inpatients with suspected or confirmed stroke from 1989 to 2000. The manufacturer also provided an alternative distribution of the proportion of people who received standard treatment in each health state from the placebo arm of the ECASS III trial at 90 days. This alternative distribution (61.54% independent, 30.27% dependent and 8.19% dead) was used by the ERG in exploratory sensitivity analyses. The manufacturer then used the relative risks of death and death or dependence to calculate the distribution of people in the alteplase arm across the independent, dependent and dead states at the end of the first phase (6 months). The manufacturer used the relative risk of death to estimate the proportion of people who would die and therefore enter the dead state during the first phase. The proportion of people in the dependent state at 6 months was calculated as the difference between the estimated proportion of people who were dead or dependent, and the estimated proportion who were dead. The manufacturer assumed in the model that a symptomatic intracranial haemorrhage had a cost impact (because it required a further diagnostic computed tomography [CT] scan), with the health

consequences being captured in the outcome of death or dependence from the clinical trials.

- 3.14 For the second phase of the model (6 to 12 months), the manufacturer assumed that people could move from the independent or dependent state to any other health state with equal probabilities for both treatment arms. These transition probabilities were based on the Lothian stroke registry. For the third phase of the model (beyond 12 months), the annual risk of a recurrent stroke (0.05), and the associated risk of mortality (0.25), were taken from the Lothian stroke registry. To estimate the mortality risk for people who did not have another stroke, the manufacturer took data from the Office for National Statistics life tables for England and Wales and adjusted them upward by a factor of 2.3 (taken from the Perth Community Stroke Study) to reflect the higher mortality rates among people who have had a stroke compared with the general UK population.
- 3.15 The manufacturer conducted a literature review to identify appropriate utility values for the independent and dependent states in the model. The manufacturer did not identify any relevant utility values additional to those used in NICE technology appraisal guidance 122 on alteplase in acute ischaemic stroke within the first 3 hours after symptom onset. The manufacturer's submission for this appraisal identified 1 trial (Dorman et al., 1997) that collected EQ-5D utility values in a sample of 147 patients from the Lothian stroke registry. This trial provided utility values of 0.74 (95% CI 0.69 to 0.79) for the independent state and 0.38 (95% CI 0.29 to 0.47) for the dependent state. The model assumed that these utility values remained fixed over time unless a person had a recurrent stroke which resulted in dependency, and thus a move from the independent to the dependent state.

- 3.16 The model included drug acquisition and administration costs as well as the costs of acute and long-term stroke care. The cost of alteplase was based on the mean body weight (76 kg) of patients in the 3 to 4.5-hour cohort from the SITS-MOST trial. Based on the recommended dose of 0.9 mg/kg, the average dose was 68.4 mg, resulting in a total estimated cost of £480 (£300 per 50-mg pack and £180 per 20-mg pack). Administration costs associated with alteplase of £1316 per patient were based on estimates of extra staff time in the trial by Sandercock et al. (2002). For people in either treatment arm who had a symptomatic intracranial haemorrhage, the model included a one-off cost of £100 for an additional CT scan. For all health states in the model, the manufacturer applied annual costs specific to the state (adjusted for inflation to 2012/13 prices) adapted from a study by Youman et al. (2003), which calculated the costs of acute events and long-term stroke care.
- 3.17 The manufacturer's base-case deterministic cost-effectiveness analysis for the 0 to 4.5-hour window estimated an incremental cost-effectiveness ratio (ICER) of £2441 per quality-adjusted life year (QALY) gained for alteplase compared with standard care (incremental costs £811; incremental QALYs 0.333). The probabilistic cost-effectiveness analysis resulted in an ICER of £2296 per QALY gained.
- 3.18 The manufacturer conducted a number of one-way sensitivity analyses on various parameters in the model, including the relative risks associated with alteplase of death or of death or dependence, the risk of recurrent stroke and mortality irrespective of previous treatment, the dose of alteplase treatment, the annual costs of care in the dependent and independent states, the cost of a fatal stroke, and the utility values. The results of these one-way sensitivity

analyses indicated that the ICERs were robust to changes in most input parameters, except for the relative risks of death and death or dependence for treatment with alteplase applied in the first phase of the model. When the manufacturer used the upper limit of the 95% confidence interval for the relative risks of death (1.18) and death or dependence (0.92), alteplase treatment led to a very small loss in QALYs at a decreased cost compared with standard care, resulting in £44,342 saved per QALY lost. The manufacturer also conducted additional deterministic sensitivity analyses, which included different scenarios using additional clinical efficacy data from unplanned subgroup analyses of the ATLANTIS A and B and ECASS II trials for 3 to 4.5 hours, and weighted the results based on the assumption that in UK clinical practice a higher proportion of patients are treated during the 0 to 3-hour window (76%) than during the 3 to 4.5-hour window (24%). Using these analyses, alteplase either dominated placebo (that is, was both less costly and more effective) or had an ICER below £2000 per QALY gained. Results of the probabilistic sensitivity analysis showed that alteplase had a high probability (above 90%) of being cost effective at a level of £20,000 to £30,000 per QALY gained.

- 3.19 The manufacturer's base-case deterministic cost-effectiveness analysis for the 3 to 4.5-hour window resulted in an ICER of £6272 per QALY gained for alteplase compared with standard care (incremental costs £2068; incremental QALYs 0.33). The probabilistic cost-effectiveness analysis resulted in an ICER of £6169 per QALY gained. The results of the one-way sensitivity analyses were similar to those for the 0 to 4.5-hour window, indicating that the ICERs were robust to changes in most input parameters, except for changes in the relative risks of death and death or dependence for treatment with alteplase. In an additional sensitivity analysis, the manufacturer pooled 3 to 4.5-hour efficacy

data from the ECASS II and ATLANTIS trials with the ECASS III data. This sensitivity analysis resulted in an ICER of £5631 per QALY gained for alteplase compared with standard care.

3.20 For the 0 to 3-hour treatment window, the manufacturer presented cost-effectiveness results similar to those presented in the previous guidance on alteplase in acute ischaemic stroke (NICE technology appraisal guidance 122); that is, alteplase dominated standard care, resulting in lower costs and more QALYs for both the deterministic and the probabilistic analyses.

3.21 The ERG considered that the clinical-effectiveness evidence submitted by the manufacturer was of good quality. The ERG noted that the patients randomised to the alteplase arm of both the NINDS trial (which provided clinical evidence for the 0 to 3-hour window) and the ECASS III trial had strokes that were less severe on average, which in turn may have biased the results in favour of alteplase. However, the manufacturer also presented adjusted analyses for the primary outcome (disability at 90 days) from the ECASS III trial. The ERG considered that the meta-analytical approach by the manufacturer was appropriate. The ERG agreed with the manufacturer that data derived from unplanned subgroup analyses from the ATLANTIS A and B and ECASS II trials, in which treatment with alteplase was administered up to 6 hours from onset of symptoms, should not be included in the base-case meta-analyses. The ERG also noted that heterogeneity between the studies included in the base-case meta-analyses for the 0 to 4.5-hour window for the outcomes of death and death or dependence was low and not statistically significant.

3.22 The ERG commented that the manufacturer submitted an economic model that was in line with the decision problem defined in the scope and closely adhered to the NICE reference case

requirements for economic analysis. The ERG commented that the manufacturer provided a reasonable strategy for searching the literature for existing cost-effectiveness studies, although it did not explicitly state its exclusion criteria. The ERG stated that it was appropriate for the manufacturer to conduct separate analyses for patients eligible for treatment within the 0 to 3-hour window and the 3 to 4.5-hour window. The ERG noted that the utility values for the dependent and independent states did not allow for any decreases in health-related quality of life over time, which may have overestimated the lifetime QALYs accrued in the independent state. The ERG stated that, although this may have biased the QALY gains in favour of alteplase, the manufacturer's economic model was not sensitive to changes in the utility values, and so the effect of adjusting these values over time in the model was likely to be small. The ERG noted that in the probabilistic sensitivity analysis, the manufacturer sampled independently the relative risks for death and death or dependence associated with treatment with alteplase, which had a marked impact on the ICERs in the one-way sensitivity analyses. The ERG noted that this did not take into account the likely correlation between the outcomes of death and death or dependence, and that the probabilistic sensitivity analysis might not provide an accurate description of the uncertainty around the mean costs and QALYs, although the ERG did not expect it to have a large impact on the ICER.

- 3.23 The ERG conducted an exploratory sensitivity analysis by replacing the proportion of people in the 3 health states (dependent, independent and dead) at the end of the first phase (0 to 6 months) taken from the Lothian stroke registry with those observed in the ECASS III trial population. Because mortality rates were lower in the ECASS III trial, a higher proportion of patients were in the independent state (61.54%) and a lower proportion in the dead

state (8.19%). This sensitivity analysis resulted in an ICER of £4451 per QALY gained for alteplase compared with standard care for the 0 to 4.5-hour window (incremental costs £698; incremental QALYs 0.157).

- 3.24 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

- 4.1 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.
- 4.2 The Committee discussed the place of alteplase in the clinical pathway for people who have had an acute ischaemic stroke. The Committee heard from the clinical specialists that alteplase is routinely used in the NHS in England and Wales in patients aged 18–80 years within 4.5 hours of onset of symptoms. The Committee was aware of the recently published third International Stroke Trial (IST-3), an open-label trial comparing alteplase with standard care. However, the Committee noted that the manufacturer had excluded this trial from its submission because it provided data that were not restricted to alteplase within its current UK marketing authorisation; specifically, the trial included patients aged above 80 years and patients who were treated up to 6 hours after the onset of symptoms.

- 4.3 The Committee heard from clinical specialists that alteplase is more effective the earlier it is given to patients. The clinical specialists commented that, while extending the treatment window to 4.5 hours would enable more patients to be treated with alteplase, this might result in some patients who present early receiving delayed treatment and therefore not benefiting from alteplase to the extent that they might otherwise have. The clinical specialists and patient experts emphasised the importance of treating patients with acute ischaemic stroke as early as possible.
- 4.4 The Committee heard from the patient experts that an important benefit of alteplase was its potential to reduce long-term disability caused by stroke, which can affect the quality of life of the patient and their families, carers and friends, and can also increase the need to adjust the patient's lifestyle and living conditions. The Committee was aware that brain imaging must be carried out to confirm absence of intracranial bleeding before treatment with alteplase can be started. However, the Committee heard from 1 patient expert that some people with acute ischaemic stroke may not have immediate access to brain imaging facilities. The Committee recognised the importance of this issue, and noted the NICE Quality Standard for Stroke, which recommends that patients with acute stroke receive brain imaging within 1 hour of arrival at hospital. The Committee also heard from clinical specialists that Accident and Emergency departments of all acute-care hospitals in England and Wales should have access to 24-hour, 7 days a week brain-imaging facilities. The Committee recognised that patients outside the licensed indication for alteplase (under 18 years and over 80 years of age) in England and Wales may have the potential to benefit from treatment with the technology. However, consistent with NICE methods, the Committee was aware that it can only

make recommendations based on the current marketing authorisation for alteplase.

- 4.5 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 that included in NICE technology appraisal guidance 122 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 heard from clinical specialists that, although the trial included only a small proportion of patients from the UK, the results of the trial were generalisable to patients receiving alteplase treatment in England and Wales. The Committee also heard from the clinical specialists that it was reasonable for the manufacturer to measure the effectiveness of alteplase from analyses that adjusted for baseline differences in potential confounding variables between the 2 treatment groups. In addition, the clinical specialists noted that the modified Rankin scale was widely used as a measure of disability in stroke patients in England and Wales. The Committee concluded that the ECASS III 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.
- 4.6 The Committee considered the clinical effectiveness of alteplase for the 3 to 4.5-hour treatment window. The Committee noted that no statistically significant differences in mortality, or in the composite outcome of death or dependence, between patients randomised to alteplase or standard care were observed at 90-day follow-up. However, the Committee also noted that a statistically significantly higher proportion of patients in the alteplase treatment arm achieved a favourable outcome without significant disability

(modified Rankin scale score of 0 or 1) at 90-day follow-up. The Committee therefore concluded that alteplase administered between 3 and 4.5 hours after onset of stroke symptoms was an effective treatment for acute ischaemic stroke in decreasing the probability of disability.

- 4.7 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 (modified Rankin scale 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 noted that there were no statistically significant differences in all-cause mortality reported at 90 days between alteplase and placebo for any of the three treatment windows. Therefore, the Committee agreed that an effect of alteplase on improving survival has currently not been proven. The Committee noted that a statistically significant difference in favour of alteplase was reported for the composite outcome of death or dependence for the 0 to 3-hour and 0 to 4.5-hour treatment windows in the manufacturer's meta-analyses. The Committee therefore 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.

- 4.8 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 symptomatic

intracranial haemorrhage 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 symptomatic intracranial haemorrhage, the absolute number of patients in the ECASS III trial who had a symptomatic intracranial haemorrhage was small. The Committee heard from the clinical specialists that symptomatic intracranial haemorrhage 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 symptomatic intracranial haemorrhage associated with alteplase is offset by significant improvements in favourable outcomes at 90 days, symptomatic intracranial haemorrhage is an adverse event that needs to be included in modelling of the cost effectiveness of alteplase.

- 4.9 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 122 (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 symptomatic intracranial haemorrhage 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.

- 4.10 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 the

results were robust for most of the deterministic sensitivity analyses conducted by the manufacturer. The Committee also noted that none of the additional exploratory analyses undertaken by the ERG resulted in ICERs that varied substantially from those presented in the manufacturer's submission. The Committee considered that patients with acute ischaemic stroke who are admitted to hospital later (beyond 3 hours after onset of symptoms) may have less severe stroke and so any absolute benefit of treatment with alteplase compared with standard care may be diminished, resulting in a higher ICER. However, the Committee noted that the ICER for the 3 to 4.5-hour treatment window was low and therefore 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. 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.

- 4.11 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.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Alteplase for treating acute ischaemic stroke (review of technology appraisal guidance 122)	Section
Key conclusion		
<p>Alteplase is recommended within its marketing authorisation for treating acute ischaemic stroke in adults, if:</p> <ul style="list-style-type: none"> 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. 		1.1
<p>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 in decreasing the probability of disability.</p>		4.6
<p>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.</p>		4.7
<p>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.</p>		4.10
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialists that alteplase is routinely used for the treatment of acute ischaemic stroke in the NHS in England and Wales in patients aged 18–80 years within 4.5 hours of onset of symptoms.	4.2

The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee heard from the patient experts that an important benefit of alteplase was its potential to reduce long-term disability caused by stroke, which can affect the quality of life of the patient and their families, carers and friends, and can also increase the need to adjust the patient's lifestyle and living conditions.</p>	4.4
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>A UK marketing authorisation for alteplase to treat acute ischaemic stroke within 3 hours of the onset of symptoms was granted in September 2002. On 14 March 2012 the manufacturer received approval from the Medicines and Healthcare products Regulatory Agency extending the use of alteplase to within 4.5 hours of the onset of symptoms. The current marketing authorisation states that treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques.</p>	2.1
<p>Adverse reactions</p>	<p>The Committee noted that a significantly higher proportion of patients in the alteplase arm had symptomatic intracranial haemorrhage 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 symptomatic intracranial haemorrhage, the absolute number of patients in the ECASS III trial who had a symptomatic intracranial haemorrhage was small. The Committee concluded that, although the increased risk of symptomatic intracranial haemorrhage associated with alteplase is offset by significant improvements in favourable outcomes at 90 days, symptomatic intracranial haemorrhage is an adverse event that needs to be included in modelling of the cost effectiveness of alteplase.</p>	4.8

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The Committee noted that no clinical-effectiveness data for the 0 to 3-hour treatment window additional to that included in NICE technology appraisal guidance 122 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 concluded that the ECASS III 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.</p> <p>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.</p>	<p>4.5</p> <p>4.7</p>
Relevance to general clinical practice in the NHS	<p>The Committee recognised that patients outside the licensed indication for alteplase (under 18 years and over 80 years of age) in England and Wales may have the potential to benefit from treatment with the technology. However, consistent with NICE methods, the Committee was aware that it can only make recommendations based on the current marketing authorisation for alteplase.</p>	4.4
Uncertainties generated by the evidence	<p>The Committee noted that there were no statistically significant differences in all-cause mortality reported at 90 days between alteplase and placebo for any of the three treatment windows. Therefore, the Committee agreed that an effect of alteplase on improving survival has currently not been proven.</p>	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable	–

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>From intention-to-treat analyses in the ECASS III trial, 52.4% of patients randomised to the alteplase treatment arm had a favourable outcome at 90 days (a modified Rankin score of 0 or 1 [no significant disability]) compared with 45.2% of patients randomised to placebo (OR 1.34, 95% CI 1.02 to 1.76, p=0.04).</p> <p>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 in decreasing the probability of disability.</p> <p>The Committee noted that a statistically significant difference in favour of alteplase was reported for the composite outcome of death or dependence for the 0 to 3-hour and 0 to 4.5-hour treatment windows in the manufacturer’s meta-analyses. The Committee therefore 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.</p>	<p>3.4</p> <p>4.6</p> <p>4.7</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>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 122 (0 to 3-hour window) and agreed that this approach was appropriate. The Committee concluded that the economic model adhered to the NICE reference case for economic analysis and the modelling approach was reasonable.</p>	<p>4.9</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>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.</p>	<p>4.9</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>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 symptomatic intracranial haemorrhage 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.</p>	<p>4.9</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Not applicable</p>	<p>–</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The ICERs were robust to changes in most input parameters, except for the relative risks of death and death or dependence for treatment with alteplase applied in the first phase of the model.</p>	<p>3.18</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>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.</p>	<p>4.10</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>Not applicable</p>	<p>–</p>
<p>End-of-life considerations</p>	<p>Not applicable</p>	<p>–</p>
<p>Equalities considerations and social value judgements</p>	<p>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.</p>	<p>4.11</p>

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Proposed recommendations for further research

- 6.1 The clinical efficacy and safety of thrombolysis with alteplase for acute ischaemic stroke is being assessed outside of its current marketing authorisation, specifically in patients aged up to 80 years and up to 6 hours from onset of stroke symptoms (the third International Stroke Trial [IST-3]).

7 Related NICE guidance

Published

- [Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events \(review of technology appraisal guidance 90\)](#). NICE technology appraisal guidance 210 (2010).
- [Prevention of cardiovascular disease](#). NICE public health guidance 25 (2010).
- [Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack \(TIA\)](#). NICE clinical guideline 68 (2008).
- [Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease](#). NICE clinical guideline 67 (2008).
- [Alteplase for the treatment of acute ischaemic stroke](#). NICE technology appraisal guidance 122 (2007).

8 Proposed date for review of guidance

- 8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in September 2015. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee B
August 2012

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director - Pharmaceuticals & Personal Health, Oral Care Europe

Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Eleanor Grey

Lay member

Dr Neil Iosson

General Practitioner

Terence Lewis

Lay Member

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Rubin Minhas

General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Elizabeth Murray

Reader in Primary Care, University College London

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr John Rodriguez

Assistant Director of Public Health, NHS Eastern and Coastal Kent

Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Cliff Snelling

Lay Member

Marta Soares

Research Fellow, Centre for Health Economics, University of York

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology,
University of Birmingham

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

B NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Matthew Dyer

Technical Lead

Kay Nolan

Technical Adviser

Jeremy Powell

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (SchARR), The University of Sheffield:

- Davis S, Holmes M, Simpson E, et al. Alteplase for the treatment of acute ischaemic stroke (review of technology appraisal 122), May 2012

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on alteplase by providing a written statement to the Committee. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Boehringer Ingelheim

II Professional/specialist and patient/carer groups:

- AntiCoagulation Europe UK
- Association of British Neurologists
- British Geriatrics Society
- College of Emergency Medicine
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Healthcare Improvement Scotland
- Medical Research Council

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on alteplase by providing oral evidence to the Committee.

- Professor John Potter, Professor of Ageing and Stroke, University of East Anglia, nominated by the British Geriatric Society – clinical specialist
- Professor Peter Sandercock, Professor of Medical Neurology, Western General Hospital, nominated by the Association of British Neurologists – clinical specialist
- Dr Gavin Young, Consultant Neurologist, South Tees NHS Foundation Trust, nominated by the NICE Clinical Guidelines – clinical specialist
- Joanie Scott, nominated by the Stroke Association – patient expert
- Robert Yexley, nominated by the Stroke Association – patient expert

D Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Boehringer Ingelheim