

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

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**Final scope issued by NICE    Decision problem**

## Key issues for consideration

### Clinical effectiveness

The ERG noted that both the NINDS trial, which provided most of the clinical evidence for the 0–3 hour window, and the ECASS III trial, which provided most of the clinical evidence for the 3–4.5 hour treatment window, had imbalances in baseline stroke severity (a key prognostic factor) in favour of alteplase. Does the Committee have any concerns about the extent to which these imbalances may influence the clinical outcomes in both trials and the results of the manufacturer's meta-analyses?

The clinical efficacy evidence for the 3–4.5 hour treatment window was provided primarily from the ECASS III trial, in which 22 of 821 patients were recruited in the UK. Does the Committee consider that the results of this study can be generalised to clinical practice in the NHS in England and Wales?

### Cost effectiveness

The main drivers of the manufacturer's cost-effectiveness analysis were the relative risks of death and 'death or dependency'. However, the ERG noted

that the probabilistic sensitivity analysis did not account for any correlation between these two outcomes, and therefore did not provide an accurate description of the uncertainty around the mean costs and quality-adjusted life years (QALYs). Does the Committee consider the results of the manufacturer's probabilistic sensitivity analysis to be valid?

## **1 Background: clinical need and practice**

1.1 The word stroke refers to the clinical syndrome that occurs when there is an interruption of the blood supply to a localised area of the brain. There are two main types of stroke – ischaemic and haemorrhagic. An ischaemic stroke arises when there is a blockage in a blood vessel serving the brain caused by a blood clot (thrombus). A haemorrhagic stroke occurs when a blood vessel in or around the brain ruptures causing blood to leak out. Over 80% of strokes are ischaemic.

1.2 According to the UK Stroke Association, more than 130,000 people in England and Wales have a stroke each year. Mortality statistics from 2009 indicate that approximately 43,000 people died from stroke (ischaemic and haemorrhagic) in England and Wales. More than 450,000 people in England are severely disabled as a result of stroke in England.

1.3 Standard treatment for stroke includes supportive and medical management in a specialist centre during the acute phase (including thrombolysis if appropriate to break up blood clots), measures to prevent the damage to the brain from getting worse, and appropriate rehabilitative and physiotherapy programmes during the post-stroke period. 'Alteplase for the treatment of acute ischaemic stroke' (NICE technology appraisal 122) and 'Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack' (NICE clinical guideline 68) recommend

thrombolysis with alteplase within its marketing authorisation (which until 14 March 2012 was within 3 hours of symptom onset) for adults with acute ischaemic stroke. Alteplase should only be used by physicians trained and experienced in using thrombolytic treatments and with the facilities to monitor that use.

## **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 which 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 (MHRA) for alteplase use to be extended to within 4.5 hours of the onset of symptoms.

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. Based on a recommended dose of 0.9 mg per kilogram of body weight, this

cost can range from £300 to £600. Costs may vary in different settings because of negotiated procurement discounts.

### **3 Remit and decision problem(s)**

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of alteplase within its licensed indication for the treatment of acute ischaemic stroke (review of existing NICE guidance TA 122).

## Table 1. Decision problem addressed in submission

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<b>Intervention</b>	Alteplase	Alteplase (administered as per the licensed dosage and technique detailed in the summary of product characteristics)
<b>Comparators</b>	Standard medical and supportive management that does not include alteplase.	The standard medical care that does not include alteplase – there are no other drugs licensed for thrombolysis in this indication. Placebo is used as proxy for no treatment. Alteplase treatment is additive to current care.
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> disability (modified Rankin scale)</li> <li><input type="checkbox"/> functional recovery</li> <li><input type="checkbox"/> neurological deficit</li> <li><input type="checkbox"/> change in mental health, including anxiety and depression</li> <li><input type="checkbox"/> mortality</li> <li><input type="checkbox"/> length of hospital stay</li> <li><input type="checkbox"/> adverse effects of treatment, including bleeding events</li> <li><input type="checkbox"/> health-related quality of life.</li> </ul>	<p>The outcomes addressed are:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> disability (modified Rankin scale)</li> <li><input type="checkbox"/> functional recovery</li> <li><input type="checkbox"/> neurological deficit</li> <li><input type="checkbox"/> mortality</li> <li><input type="checkbox"/> length of hospital stay</li> <li><input type="checkbox"/> adverse effects of treatment, including bleeding events</li> <li><input type="checkbox"/> health-related quality of life.</li> </ul> <p>Mental health outcomes are not addressed in the submission.</p>
<b>Economic evaluation</b>	<p>The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY).</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from</p>	<p>Cost-effectiveness has been expressed in terms of cost per QALY.</p> <p>A life-time time horizon has been employed to capture the chronic nature of disability associated with stroke and any mortality differences.</p> <p>Costs have been considered from an NHS and personal social services perspective.</p>

3.2 According to the manufacturer, treatment with alteplase is provided in addition to standard care for stroke. Standard care includes supportive and medical management. To be eligible for treatment with alteplase, the patient has to be examined rapidly in consultation with stroke specialists with immediate computed tomography (CT) scanning of the head. Alteplase must be administered within 4.5 hours of the onset of stroke symptoms.

## **4 Clinical-effectiveness evidence**

4.1 The manufacturer carried out a systematic literature search, which was based on a previously published Cochrane review ('Thrombolysis for acute ischaemic stroke') but restricted to the use of alteplase within its UK marketing authorisation. For the 0–3 hour treatment window, no trials additional to those included in 2007 in the current guidance on alteplase in acute ischaemic stroke (NICE technology appraisal guidance 122) were identified. The trials in technology appraisal 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 of these trials were double-blinded, placebo-controlled randomised controlled trials with alteplase administered at its licensed dose of 0.9 mg/kg. Treatment with alteplase was administered either 0–6 hours after onset of symptoms (ATLANTIS A and B, ECASS II), or 0–3 hours after onset of symptoms (NINDS I and II) and follow-up was up to 90 days. The NINDS and ATLANTIS trials were multicentre trials conducted in North America and ECASS II was a multicentre study conducted across multiple sites in Europe (including the UK), Australia and New Zealand.

4.2 The clinical effectiveness evidence in the manufacturer's submission focused on the extended 3–4.5 hour treatment window. For this treatment window, the only directly relevant trial identified by the manufacturer was ECASS III. Other trials with data relevant to this treatment window (0–6 hours after symptom onset) included ATLANTIS A and B and ECASS II. The manufacturer also briefly mentioned the IST-3 ('Third international stroke trial') study, a randomised open-label blinded endpoint study 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 study selection criteria and that no published results were available at the time of submission.

4.3 The manufacturer's clinical-effectiveness evidence for the 3–4.5 hour window was derived primarily from ECASS III, a placebo-controlled multi-centre trial carried out across 130 sites in 19 European countries including the UK (22 of 821 patients). Data from ATLANTIS A and B and ECASS II, which were not stratified by the 3–4.5 hour window, were also explored in sensitivity analyses. Patients were eligible for inclusion into the ECASS III study if they were aged between 18 and 80 years, were diagnosed with acute ischemic stroke, and treatment was received in the 3–4.5 hour window. Before randomisation brain imaging was used to confirm the patient did not have intracranial haemorrhage. Eligible patients were randomly assigned to receive 0.9 mg/kg of alteplase (n=418) or placebo (n=403). Study follow-up was 90 days. Baseline demographic and disease characteristics of the two treatment arms were similar, although there were statistically significant differences between the two arms (before adjustment for multiple comparisons) with respect to the initial severity of stroke and the history of previous stroke.

4.4 The primary outcome of ECASS III was disability at 90 days, as assessed by the modified Rankin scale, a 7-point progressive functionality scale (range 0–6) in which 6 is dead and 0 is symptom free. For the intention-to-treat population, 52.4% of patients in the alteplase treatment arm had a favourable outcome at 90 days (defined as a score of 0 or 1 on the modified Rankin scale), compared with 45.2% of patients in the placebo arm (odds ratio [OR] 1.34, 95% confidence interval [CI] 1.02 to 1.34,  $p=0.04$ ). After adjusting for confounding baseline variables including NIHSS (National Institutes of Health stroke scale) score, smoking status, time from onset of stroke to treatment, presence or absence of prior hypertension, and treatment arm, alteplase remained statistically significantly associated with a favourable outcome (OR 1.42, 95% CI 1.02 to 1.98,  $p=0.04$ ).

4.5 The manufacturer also presented the outcome of death or dependency (defined as a score of 3–6 on the modified Rankin scale) at 90 days from ECASS III. For the intention-to-treat population, 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). The ECASS III study also reported 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 for brain injury), a score of 95–100 on the Barthel index (a 10-item measure of a person's daily function), and a score of 0–1 on the NIHSS (a 15-item quantitative measure of stroke-related neurologic deficit). For the intention-to-treat population, the global outcome score was statistically significantly in favour of the alteplase treatment arm (OR 1.28, 95% CI 1.00 to 1.65,  $p=0.05$ ). Results for the key primary

and secondary outcomes from the ECASS III study are presented in table 2.

**Table 2. Results for primary and secondary outcomes from ECASS III at 90 days (intention-to-treat population)**

4.6 The manufacturer presented a summary of adverse reactions from the

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intention-to-treat population in the ECASS III study at 90 days. 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. Serious adverse reactions were reported for 25.1% of the alteplase arm and 24.6% of the placebo arm. Fatal adverse reactions were reported for 7.7% of the alteplase arm and 8.4% of the placebo arm. A statistically significantly higher proportion of patients in the alteplase arm had intracranial haemorrhage (27.03% compared with 17.62%,  $p=0.0012$ ) and symptomatic intracranial haemorrhage (SICH) (2.39% compared with 0.25%,  $p=0.008$ ) compared with the placebo arm. Three patients who were randomised to the alteplase arm had a fatal intracranial haemorrhage.

4.7 The manufacturer conducted meta-analyses to calculate relative risks of all-cause mortality at 90 days, death or dependency at

90 days, and SICH within 10 days for the three treatment windows (0–3 hours, 3–4.5 hours, and 0–4.5 hours). Both fixed and random-effects meta-analyses were presented, with the latter used for the clinical effectiveness parameters in the manufacturer's economic model. For the 0–4.5 hour window, data from ECASS II (0–3 hours), ECASS III (3–4.5 hours) and NINDS (0–3 hours) were used in the base-case analysis. Details of the studies included in the meta-analyses for the three outcomes along with results of the fixed and random effects models are in table 3. Heterogeneity between the three studies was low for the outcomes of all-cause mortality and death or dependency but moderate for the outcome of SICH.

4.8 For the outcome of all-cause mortality, there were no statistically significant differences reported at 90 days between alteplase and placebo for any of the three treatment windows. For the outcome of death or dependency at 90 days, a statistically significant difference in favour of alteplase was reported for the 0–3 hour window (RR 0.81, 95% CI 0.72 to 0.92,  $p=0.002$ ) and 0–4.5 hour window (RR 0.83, 95% CI 0.75 to 0.92,  $p<0.001$ ) with similar results for the sensitivity analyses. However, no statistically significant differences were reported for the 3–4.5 hour window (RR 0.87, 95% CI 0.73 to 1.05,  $p=0.14$ ). For the outcome of SICH within 10 days, a statistically significant difference in favour of placebo was reported for all three treatment windows. For the 0–4.5 hour window, heterogeneity between the studies included in the base-case analysis was low for the outcomes of all-cause mortality and death or dependency and moderate for the outcome of SICH.

**Table 3. Summary of relative risk meta-analyses for three treatment windows**

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4.9 Health-related quality of life was only reported in ECASS II, which collected SF-36 data for patients treated 0–6 hours after onset of symptoms. The study found no statistically significant treatment effect in favour of alteplase for either the physical ( $p=0.284$ ) or the mental ( $p=0.183$ ) components of the SF-36.

4.10 The manufacturer presented subgroup analyses from the ECASS III study for a favourable outcome (modified Rankin scale score 0–1), all-cause mortality and SICH according to demographic characteristics, baseline clinical data and past medical history. Statistically significant differences in favour of alteplase were found for patients with a history of stroke (modified Rankin scale score 0–1), gender and smoking history (for all-cause mortality), and for patients aged 65 years and over (for SICH). However, the manufacturer commented that these results should be treated with caution because the ECASS III study was not formally powered to detect statistically significant differences between the two treatment arms for these subgroups.

4.11 The ERG considered that the clinical-effectiveness evidence submitted by the manufacturer was of good quality. However, the ERG noted that both the NINDS trial, which provided clinical evidence for the 0–3 hour window, and the ECASS III trial had patients with lower stroke severity in the alteplase arm at baseline, which may have biased results in favour of alteplase, although adjusted analyses for the primary outcome were presented for the ECASS III trial. The ERG considered that the meta-analytical approach by the manufacturer was appropriate and noted that both fixed and random effects analyses were provided. The ERG agreed with the manufacturer that data derived from ad-hoc subgroup analyses from the ATLANTIS A and B and ECASS II trials should be excluded from the base-case meta-analyses. The ERG also

noted that heterogeneity between the studies included in the base-case meta-analyses for the 0–4.5 hour window, which combined data from across the 0–3 and 3–4.5 hour windows, was neither large nor statistically significant.

## **5 Comments from other consultees**

5.1 Statements from patient groups indicated that people who are eligible for alteplase treatment will benefit from a potential reduction in the impact of damage to the brain, which can affect the ability to communicate, mobility (because of paralysis) and mental processes, and cause dysphagia, incontinence and visual impairment. It was noted that long-term disability caused by stroke can affect the quality of life of both patient and their families and that radical adjustments to lifestyle and living conditions may be needed. It was also noted that people of working age who have a stroke may face further disadvantage if they are no longer able to work.

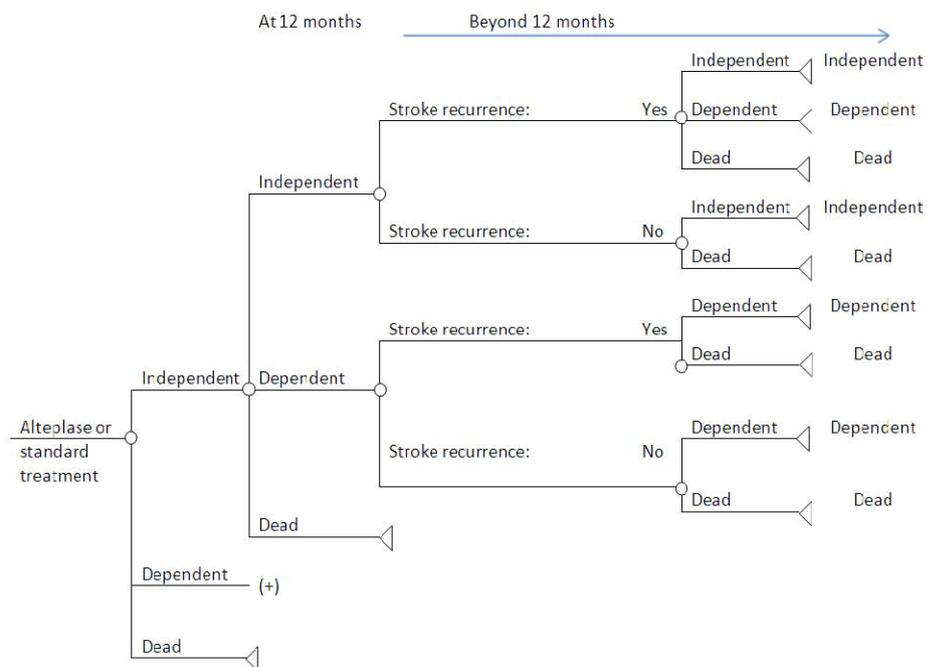
5.2 No comments were received from professional groups or NHS organisations.

## **6 Cost-effectiveness evidence**

6.1 The manufacturer performed 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 the 3–4.5 hour window of symptom onset. In the current guidance on alteplase in acute ischaemic stroke (NICE technology appraisal guidance 122) the manufacturer identified one cost-effectiveness analysis (Sandercock et al., 2002) that was relevant to the decision problem and was subsequently adapted as part of the manufacturer's submission.

6.2 For this review, the manufacturer adapted the economic model that was developed by Sandercock et al. and used in NICE technology appraisal guidance 122 (0–3 hour window) by incorporating clinical efficacy data for the 3–4.5 hour treatment window from the ECASS III study. A Markov model with three possible health states (independent, dependent and dead) was used to evaluate the lifetime impact of standard treatment compared with treatment with alteplase within 4.5 hours of the onset of stroke symptoms. The model was split into three phases: from 0 to 6 months people with acute ischaemic stroke entered the model and the treatment effect of alteplase was applied; from 6 to 12 months no treatment effect was applied; and beyond 12 months people could have a recurrent stroke before moving to the independent, dependent or dead states. The model assumed a cycle length of 6 months for the first 12 months, followed by 12-monthly cycles thereafter. The model schematic is presented in Figure 1.

**Figure 1. Schematic of manufacturer’s economic model**



6.3 The population used in the model was based on SITS-MOST ('Safe implementation of thrombolysis in stroke-monitoring study'), a European observational study of patients receiving alteplase who were assumed to be representative, in terms of age (68 years) and gender (39.8% female), of patients who would receive alteplase in clinical practice in England and Wales. The model assumed that in the first phase the alteplase treatment effect was complete at 90 days and maintained at 6 months. The model also assumed that people in the dependent state at 12 months and beyond were unable to move to an independent state and that people in the independent state at 12 months and beyond were unable to move to a dependent state unless they survived a recurrent stroke. The independent state was defined by a modified Rankin scale score of 0–2 and the dependent state was defined by a modified Rankin scale score of 3–5.

6.4 The key clinical efficacy parameters for the first phase (0–6 months) of the economic model were informed by the manufacturer's meta-analyses for the three treatment windows and are summarised in table 4. As mentioned previously, data from patient subgroups in from the ATLANTIS A and B trials (0–3 hours and 0–4.5 hours) and ECASS II trial (3–4.5 hours) were also included as part of the sensitivity analyses. The distribution of people in the independent, dependent and death states in the first phase in the standard treatment arm of the model was informed by the Lothian stroke registry, a registry of 1779 patients in Scotland who needed inpatient care because of suspected or confirmed stroke from 1989 to 2000. The manufacturer also provided the distribution of health states for the placebo arm of the ECASS III trial at 90 days, which were used in exploratory sensitivity analyses conducted by the ERG. The relative risks of death and death or

dependency were then used to modify the distribution of people in the independent, dependent and death states in the standard care arm for the first phase of the model. The relative risk of death was applied to the death state and the relative risk of death or dependency was applied to the dependent state. The proportion of people in the independent state for the alteplase arm was then calculated as the difference between these two states. The proportion of people having a SICH, which was taken from the ECASS III trial (3–4.5 hour window) and the manufacturer’s meta-analyses (0–3 and 0–4.5 hour windows), were assumed to have an impact on costs but no further impact on health-related quality of life in the model.

**Table 4. Key clinical efficacy parameters used in the manufacturer’s base-case economic analysis**

6.5 For the second phase of the model (6–12 months) it was assumed that people could move from any health state to another (except from the ‘dead’ state) with equal probabilities for both treatment

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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 also taken from the Lothian stroke register. For people who did not have a recurrent stroke, age and gender-specific annual mortality rates (taken from the Office for National Statistics life tables for England and Wales) were adjusted by a stroke multiplier of 2.3 taken from a separate study (the Perth stroke study) to reflect the higher mortality rates among people who have had a stroke compared with the general UK population.

6.6 The manufacturer conducted a literature review to identify appropriate utility values for the independent and dependent states in the model. The manufacturer stated that it had not identified any additional relevant utility values other than those in the current guidance on alteplase in acute ischaemic stroke (NICE technology appraisal guidance 122). The manufacturer's submission for this appraisal identified one study (Dorman et al., 1997) that collected EQ-5D utility values in a sample of 147 Lothian stroke registry patients. This study 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 recurrent stroke resulted in transition from the independent to the dependent state.

6.7 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 3–4.5 hour cohort from the SITS-MOST study. 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, which were based on estimates of extra staff time from the study by Sandercock et al., were also included in the model. For people in either treatment arm who had a SICH, a one-off cost of £100 for an additional CT scan was included. For the independent, dependent and dead states in the model, the manufacturer applied costs from a study by Youman et al. (2003), which calculated the 3-month cost of acute events and long-term stroke care. This resulted in total annual costs for the independent and dependent states in the first and subsequent years as well as the cost of a fatal stroke event.

6.8 The manufacturer's base-case deterministic cost-effectiveness analysis (see table 5) for the 0–4.5 hour window resulted in an incremental cost-effectiveness ratio (ICER) of £2441 per 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.

**Table 5. Manufacturer's base-case deterministic results (0–4.5 hour window)**

6.9 The manufacturer conducted a number of one-way sensitivity analyses on various model parameters (see table 6). The results of these one-way sensitivity analyses indicated that the ICERs were fairly robust to changes in most input parameters, except for the relative risks of death and death or dependency. Using the higher

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95% CI for the relative risks of death and death or dependency, the standard care arm gained more QALYs at an increased cost compared with alteplase, resulting in an ICER of £44,342 per QALY gained for standard care compared with alteplase. The manufacturer also conducted additional deterministic sensitivity analyses, which included the results of ATLANTIS A and B from the pooled meta-analyses, and applied proportionate weighting based on a higher proportion (74%) of patients treated in the 0–3 hour window than in the 3–4.5 hour window (26%). For these analyses, alteplase either dominated placebo or the ICER was below £2000 per QALY gained. Results of the probabilistic sensitivity analysis showed that, at a cost-effectiveness threshold of range of £20,000 to £30,000 per QALY gained, alteplase had the highest probability of being cost effective.

Table 6. Results of manufacturer’s one-way sensitivity analyses (0–4.5 hour window)

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<b>Population</b>		Adults with acute ischaemic stroke within 4.5 hours of symptom onset
<b>Intervention</b>	Alteplase	Alteplase (administered as per the licensed dosage and technique detailed in the summary of product characteristics)
<b>Comparators</b>	Standard medical and supportive management that does not include alteplase.	The standard medical care that does not include alteplase – there are no other drugs licensed for thrombolysis in this indication. Placebo is used as proxy for no treatment. Alteplase treatment is additive to current care.
<b>Outcomes</b>	The outcome measures to be considered include: <input type="checkbox"/> disability (modified Rankin scale) <input type="checkbox"/> functional recovery <input type="checkbox"/> neurological deficit <input type="checkbox"/> change in mental health, including anxiety and depression <input type="checkbox"/> mortality <input type="checkbox"/> length of hospital stay <input type="checkbox"/> adverse effects of treatment, including bleeding events <input type="checkbox"/> health-related quality of life.	The outcomes addressed are: <input type="checkbox"/> disability (modified Rankin scale) <input type="checkbox"/> functional recovery <input type="checkbox"/> neurological deficit <input type="checkbox"/> mortality <input type="checkbox"/> length of hospital stay <input type="checkbox"/> adverse effects of treatment, including bleeding events <input type="checkbox"/> health-related quality of life.  Mental health outcomes are not addressed in the submission.

6.10 The manufacturer’s base-case deterministic cost-effectiveness analysis (see table 7) for the 3–4.5 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 0–4.5 hour window,

indicating that the ICERs were fairly robust to changes in most input parameters, except for the relative risks of death and death or dependency. In an additional sensitivity analysis, the manufacturer pooled ad-hoc 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.

**Table 7. Manufacturer’s base-case deterministic results (3–4.5 hour window)**

6.11 The manufacturer also presented updated cost-effectiveness results for the 0–3 hour window, which were very similar to those presented in the current guidance on alteplase in acute ischaemic stroke (NICE technology appraisal guidance 122). Alteplase dominated standard care, resulting in lower costs and higher QALYs for both the deterministic and

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

<b>Population</b>	<b>Final scope issued by NICE</b>	<b>Decision problem addressed in the submission</b>
		Adults with acute ischaemic stroke within 4.5

probabilistic analyses.

6.12 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 search strategy used in the manufacturer’s review of cost-effectiveness studies was appropriate, although the manufacturer did not say whether a published methodological search filter was used and did not explicitly state the exclusion criteria. The ERG

considered that it was appropriate for the manufacturer to conduct separate analyses for the subgroup of patients who are eligible for treatment within the 0–3 hour window and the subgroup who are eligible for treatment within the 3–4.5 hour window. The ERG noted that the relative risks for death and death or dependency, which had a significant impact on the ICERs in the one-way sensitivity analyses, were sampled independently in the probabilistic sensitivity analysis and therefore ignored the correlation that was likely to exist between the two outcomes. The ERG commented that this may mean that the probabilistic sensitivity analysis does not provide an accurate description of the uncertainty around the mean costs and QALYs, although it was not expected to have a large impact on the ICER.

6.13 The ERG conducted an exploratory sensitivity analysis by replacing the 6-month health states from the Lothian stroke registry with those from the ECASS III study. Because mortality rates were lower in the ECASS III study, this resulted in a higher proportion of patients in the independent state (0.6154) and a lower proportion of patients in the dead state (0.0819). This sensitivity analysis resulted in an ICER of £4451 per QALY gained for alteplase compared with standard care for the 0–4.5 hour window (incremental costs £698; incremental QALYs 0.157).

6.14 Overall, the results of the manufacturer's cost-effectiveness analyses showed that alteplase either dominated standard care or had an ICER well below £20,000 per QALY gained depending on the onset time-to-treatment window considered. The results were generally robust for all sensitivity analysis conducted. None of the additional exploratory analyses undertaken by the ERG resulted in ICERs that varied substantially from those presented in the manufacturer's submission.

## **7 Equalities issues**

7.1 The manufacturer noted that published evidence shows that the incidence of stroke is higher among black people and that this is not explained by confounders such as social class, age and sex. The manufacturer also noted that a number of published studies have also suggested that incidence and outcome of stroke varies according to race, gender, social class and area of the UK. However, this issue reflects the epidemiology of stroke and is therefore not considered to be an equalities issue that needs addressing in the appraisal.

## **8 Innovation**

8.1 No case for innovation was made by the manufacturer in its submission.

## **9 Authors**

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## **Appendix A: Supporting evidence**

### ***Related NICE guidance***

#### **Published**

- 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). Available from <http://guidance.nice.org.uk/CG67>
- Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE clinical guideline 68 (2008). Available from <http://guidance.nice.org.uk/CG68>
- Alteplase for the treatment of acute ischaemic stroke. NICE technology appraisal guidance 122 (2007). Available from <http://guidance.nice.org.uk/TA122>
- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90). NICE technology appraisal guidance 210 (2010). Available from <http://guidance.nice.org.uk/TA210>
- Prevention of cardiovascular disease. NICE public health guidance 25 (2010). Available from <http://guidance.nice.org.uk/PH25>

#### **NICE technology appraisal guidance 122**

1.1 Alteplase is recommended for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation.

#### **NICE pathways**

- There is a NICE pathway on stroke, which is available from <http://pathways.nice.org.uk/pathways/stroke>