

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final Appraisal Determination

### Alteplase for the treatment of acute ischaemic stroke

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

## **1 Guidance**

- 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.

## **2 The technology**

- 2.1 Alteplase (Actilyse, Boehringer Ingelheim Limited) has a marketing authorisation for the fibrinolytic treatment of acute ischaemic stroke. Treatment must be started within 3 hours of onset of the stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques. The marketing authorisation states that treatment must be performed by a physician specialised in neurological care. It also states that alteplase should only be administered by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor that use. Alteplase is not indicated for the treatment of acute stroke in children aged under 18 years or adults

aged over 80 years. For further information about the drug refer to the summary of product characteristics (SPC).

- 2.2 Intracranial haemorrhage is the most significant adverse event associated with alteplase. For full details of side effects and contraindications, see the SPC.
- 2.3 The recommended dose of alteplase for the treatment of acute ischaemic stroke is 0.9 mg alteplase/kg body weight (maximum of 90 mg) infused intravenously over 60 minutes, with 10% of the total dose administered as an initial intravenous bolus. Alteplase (vial with powder for reconstitution and diluent) is available at a net price of £135.00 for the 10-mg vial, £180.00 for the 20-mg vial and £300.00 for the 50-mg vial (excluding VAT; 'British national formulary' [BNF] edition 53). The drug cost varies from patient to patient because the dose is adjusted to each patient's body weight. For example, for a person weighing 75 kg, the cost of alteplase would be £480, corresponding to one vial of 20 mg and one of 50 mg to attain a dose of 67.5 mg. Costs may also 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).

- 3.1 The manufacturer's submission approached the decision problem by comparing alteplase with placebo, both given in addition to supportive and medical management. The population under consideration was adult patients with acute ischaemic stroke within 3 hours of the onset of stroke symptoms, in line with the marketing authorisation. The main outcomes considered were dependency, mortality and symptomatic intracranial haemorrhage.

- 3.2 The manufacturer identified six relevant randomised controlled trials (RCTs) of alteplase in the treatment of acute ischaemic stroke (NINDS I and II, N = 624; ATLANTIS A, N = 142; ATLANTIS B, N = 613; ECASS I, N = 620; and ECASS II, N = 814). All RCTs adopted an intention-to-treat analysis and were placebo controlled. Despite some variation among the protocols, the trials had similar patient inclusion and exclusion criteria and used comparable short- and long-term endpoints, including incidence of symptomatic intracranial haemorrhage in 7–10 days, death or dependency at 3 months, and all-cause mortality at 3 months.
- 3.3 The manufacturer's submission draws on evidence from the Cochrane Review (2003), which was an overall meta-analysis of the use of thrombolytics for acute ischaemic stroke. The analysis of the outcome of death or dependency at 3 months in the manufacturer's submission focused on all the trials that included patients who were treated with alteplase with an onset to treatment time up to 3 hours, including ECASS I in which an unlicensed dose was administered. The analysis showed a statistically significant difference (odds ratio [OR] 0.64; 95% confidence interval [95% CI], 0.50 to 0.83) favouring treatment with alteplase in terms of the outcome of death or dependency at 3 months. The incidence of symptomatic intracranial haemorrhage (defined as an intracranial haemorrhage that results in death or clinical deterioration) within 7–10 days was statistically significantly increased in patients receiving alteplase compared with patients receiving placebo (OR 3.13; 95% CI, 2.34 to 4.19).
- 3.4 The meta-analyses included in the manufacturer's submission showed no statistically significant difference in the incidence of death from all causes between the alteplase and placebo arms. This was the case in both the analysis of clinical effectiveness (OR 1.003; 95% CI, 0.713 to 1.41) and the meta-analysis used in the manufacturers' economic model (OR 0.97; 95% CI, 0.69 to

1.36). (In order to be consistent with the publications on which it was based, the economic model included a small pilot RCT; this was excluded from the analysis of clinical effectiveness.)

- 3.5 Several observational studies were also identified in the manufacturer's submission. In particular, SITS-MOST, a pan-European study that included 6483 patients, was considered to be the most relevant. Its aim was to assess the safety and efficacy of alteplase as thrombolytic therapy within the first 3 hours of onset of acute ischaemic stroke. SITS-MOST was a postmarketing surveillance study required by the European Medicines Agency as part of the marketing authorisation for alteplase. The study assessed the safety and efficacy profile of alteplase in clinical practice in order to allow for a comparison with the results obtained from the RCTs. The results of SITS-MOST indicated that a similar proportion of patients developed symptomatic intracranial haemorrhage (as defined by the Cochrane Review's criteria) as an adverse reaction in clinical practice as in the RCTs and confirmed that alteplase was effective when used within 3 hours of onset.
- 3.6 The ERG found that although the search strategy for clinical effectiveness in the manufacturer's submission lacked transparency, no relevant trials appeared to have been missed. The meta-analysis included in the manufacturer's submission should have been limited to those trials relating to alteplase given within its licensed indications. Because of this, ECASS I should have been excluded because it used an unlicensed dose of alteplase. It could also be argued that both ATLANTIS studies should have been excluded because they did not stratify randomisation by onset-to-treatment time. However, the ERG considered that the effect of excluding the ATLANTIS trials on any estimate of effectiveness would be small.

3.7 The ERG considered that the use of ORs in the economic model was not fully appropriate and that it would be more correct to use relative risk (RR) instead. Therefore, the ERG calculated RR values for comparison with the results presented in the manufacturer's submission and conducted a meta-analysis of the data from the patients in the NINDS, ATLANTIS A and B and ECASS II trials who had received alteplase in accordance with its marketing authorisation. That ERG's meta-analysis indicated that alteplase is associated with a statistically significant reduction in the risk of death or dependency at 3 months compared with placebo (RR 0.82; 95% CI, 0.72 to 0.93, absolute risk reduction 11%). Despite a statistically significantly increased risk of symptomatic intracranial haemorrhage in the alteplase arm within the first 7 to 10 days (RR 4.24; 95% CI, 1.52 to 11.83, absolute risk increase 6%), there was no statistically significant difference between alteplase and placebo in all-cause mortality at 3 months (RR 1.15; 95% CI, 0.62 to 2.16). However, the ERG noted that, even though there was no significant heterogeneity among trials for any outcome, evidence for the use of alteplase within the 3-hour window should be treated with extreme caution because it rests primarily on the NINDS trial, in which there was a substantial imbalance in baseline stroke severity – a key prognostic factor – that favoured alteplase.

3.8 A United States Food and Drug Administration (FDA) clinical review of alteplase published in 1996 and an independent re-analysis of NINDS trial data published in 2004, which were referenced in the ERG report, discussed subgroup analysis of the NINDS trial data. In both of these studies some subgroups were found to have a higher incidence of intracranial haemorrhage. However, the authors of the independent re-analysis concluded that there was no statistically significant evidence to suggest that for any subgroup the expected consequences of an intracranial

haemorrhage as a result of alteplase treatment outweighed the expected benefits of the treatment.

- 3.9 A state-transition cost-effectiveness model was used by the manufacturer to evaluate the lifetime impact of standard treatment compared with treatment with alteplase within 3 hours of the onset of stroke symptoms. Standard treatment was assumed to be medical treatment and supportive management within a specialist stroke unit, as defined in the National Service Framework for older people. Patients with confirmed ischaemic stroke who did not receive thrombolysis are given aspirin immediately, whereas those treated with thrombolysis receive aspirin about 24 hours later. The model assumes that there is no material difference in outcome attributed to the delay in starting aspirin in patients receiving thrombolysis.
- 3.10 The cost-effectiveness model included three health states (independent stroke, dependent stroke and death), and it assumed that a treatment effect occurs within the first 6 months of treatment. The ORs for the three health states in patients treated with alteplase were based on the Cochrane Review's meta-analysis of alteplase RCTs; the initial outcomes for patients receiving standard treatment were retrieved from the Lothian Stroke Registry. The probabilities of intracranial haemorrhage for standard treatment and alteplase treatment were taken from a pooled analysis of the NINDS, ECASS I and II and ATLANTIS A and B studies. Utility scores for the dependent and independent states were based on the responses to the EuroQoL quality-of-life questionnaire of a sample of 147 Lothian Stroke Registry patients. Costs of alteplase, administration, adverse events and rehabilitation were included.
- 3.11 Base-case results in the lifetime model in the manufacturer's submission showed that alteplase treatment for acute ischaemic stroke is more effective and less costly than standard treatment,

and that the probability is close to 1 that the incremental cost-effectiveness ratio (ICER) for alteplase is less than £20,000 per quality-adjusted life year (QALY) gained. One-way sensitivity analysis was also carried out by the manufacturer for all parameters, none of which appeared to significantly influence the results, with the highest ICER presented being just above £4000/QALY gained.

- 3.12 The ERG considered that the structure of the manufacturer's economic model was appropriate for the required analysis. However, it noted uncertainty over whether the augmented probability of a stroke recurrence in the patients who experience an intracranial haemorrhage, and the disutility and costs related to that recurrence, are fully captured by the patients entering the dependent health state. Although the use of OR was not considered suitable by the ERG, an additional analysis conducted by the manufacturer on request showed that replacing OR with RR has little impact on the results. The ERG regarded as appropriate the values used to describe extra use of resources associated with alteplase treatment and that the source data for health-related quality-of-life measures followed a similar dependence classification to that used in the economic model.
- 3.13 The ERG considered that the manufacturer's submission presented a univariate and probabilistic sensitivity analysis in which the values used for all parameters appear to be reasonable. The critical appraisal of the manufacturer's economic model undertaken by the ERG suggested that stroke management including alteplase can result in long-term cost savings and is more effective than standard treatment. However, the ERG pointed out that the economic evaluation relies heavily on the NINDS trial and, because of its baseline imbalance, the results should be treated cautiously. The ERG also noted that one important issue that was not explicitly taken into account in the economic modelling is the cost of

organisational changes required to enable treatment within the 3-hour time window.

- 3.14 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from [www.nice.org.uk/TAxxx](http://www.nice.org.uk/TAxxx)

## **4 Consideration of the evidence**

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of alteplase for the treatment of acute ischaemic stroke, having considered evidence on the nature of the condition and the value placed on the benefits of alteplase for the treatment of acute ischaemic stroke by people who have experienced an acute ischaemic stroke, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.2 The Committee considered the framing of the decision problem in the manufacturer's submission. In particular it considered the comparator. It understood from consultees that there is variability in current standard care across England and Wales. The Committee acknowledged that the RCT settings assumed that both patients who were treated with alteplase and those who received placebo had access to the same quality of care, which included prompt assessment, supportive management and careful monitoring. The Committee concluded that this would be the appropriate scenario to consider, that best supportive care and medical management without thrombolytics would be the appropriate comparator, and that this was appropriately reflected in the manufacturer's submission.

### ***Clinical effectiveness***

- 4.3 The Committee discussed the clinical effectiveness evidence presented in the manufacturer's submission. In particular it

considered the methods and results of the Cochrane Review, noting that it included data from patients in the ECASS I trial in which an unlicensed dose of alteplase was used. The Committee then considered the results of the meta-analysis conducted by the ERG for all patients treated within the marketing authorisation. It noted that alteplase, when compared with placebo, significantly reduced the risk of death or dependence after an ischaemic stroke. The Committee discussed the increased risk of early intracranial haemorrhage observed in the RCTs. It heard from clinical specialists that, in the RCTs, the definitions for the outcome measure of symptomatic intracranial haemorrhage would include many minor haemorrhages and that the incidence of clinically significant haemorrhage is somewhat lower. The Committee further noted that no statistically significant difference was found for all-cause mortality at 3 months.

- 4.4 The Committee discussed the NINDS trial in particular, because of its substantial weight in the meta-analysis results. It was aware of the concerns relating to its validity, specifically those regarding the imbalance in baseline stroke severity. The Committee noted the discussion of the NINDS study in the ERG report, including the FDA's clinical review and an independent re-analysis of the NINDS trial data. It heard opinions from clinical specialists that the results of the NINDS study are supported by RCT evidence of alteplase used beyond the 3-hour time window, and by large observational studies such as SITS-MOST. The Committee was persuaded that the issues surrounding the NINDS trial did not significantly influence the estimated benefit of alteplase. The Committee concluded that alteplase is clinically effective compared with placebo for the treatment of acute ischaemic stroke.

### ***Cost effectiveness***

- 4.5 The Committee discussed the manufacturer's economic model. It considered the model structure and the use of a lifetime timeframe to be appropriate. The Committee noted that although the ERG considered the modelling itself to be appropriate, it had expressed concerns about the clinical-effectiveness input in the cost-effectiveness analysis. The Committee was of the opinion that the sensitivity analyses of the model were sufficiently robust to generate confidence in the base-case results that alteplase is more effective and less costly than placebo (that is, best care without alteplase). The Committee therefore concluded that alteplase with best supportive care is cost effective when compared with placebo with best supportive care.
- 4.6 The Committee discussed the relevance to the economic analysis of the costs of re-organising stroke services to enable the wide use of alteplase in accordance with its marketing authorisation, such as the need for 24-hour access to computed tomography scanning and physicians with specialist interest in acute stroke care. The Committee was mindful that all patients who experience stroke would benefit from a timely assessment and a holistic approach to stroke care in a specialist centre, whether or not alteplase is a suitable treatment for them. It heard that re-organisation of stroke services is already taking place through the National Stroke Strategy. The Committee decided that it would not be appropriate to include the costs incurred in optimising services to a level which allows alteplase to be given in line with its marketing authorisation, nor for the Committee to make recommendations covering the set up of stroke centres with facilities suitable for treatment with alteplase in areas where they are not currently available.
- 4.7 The Committee discussed whether alteplase would be particularly cost effective for certain subgroups of patients. It noted that there is

evidence indicating that the earlier patients receive alteplase, the greater the benefit. However, the manufacturer's economic analysis did not demonstrate differences in cost effectiveness for different onset-to-treatment intervals. The Committee also considered whether there was available evidence that would allow identification of subgroups of patients with distinct characteristics that would predispose them to a better or worse outcome, particularly related to risk of intracranial haemorrhage, but found the available evidence to be inconclusive. The Committee concluded that alteplase has not been clearly shown to be any more or less cost effective depending on subgroup.

### ***Summary of the considerations***

- 4.8 The Committee concluded that there is evidence that alteplase plus best supportive care is clinically and cost effective compared with best supportive care alone. It emphasised the importance in its considerations of the evidence that alteplase is used only in accordance with the marketing authorisation, in particular within 3 hours after the onset of stroke symptoms and after haemorrhagic stroke has been clearly ruled out. Furthermore, because of the importance of both best practice in the overall management of acute stroke and the requirement for careful assessment of risks and benefits on an individual patient basis, the Committee put particular emphasis on considering the appropriate conditions for the use of alteplase. The Committee was aware that in the UK, physicians with experience in stroke care are not always the same as those specialised in neurological care. The Committee concluded that alteplase should be used by a physician trained and experienced in the management of acute stroke and only in centres with facilities that enable it to be used in full accordance with its marketing authorisation.

## 5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ([www.nice.org.uk/TAXxx](http://www.nice.org.uk/TAXxx)).

## 6 Recommendations for further research

- 6.1 Research is currently ongoing to evaluate the clinical effectiveness of alteplase beyond 3 hours after the onset of stroke symptoms (ECASS III and IST-3 studies). In addition, studies in patients older than 80 years would allow assessment of the clinical and cost effectiveness of alteplase in this population, which represents a

significant proportion of the patients who experience acute ischaemic stroke. Use of alteplase in both of these settings is not within the drug's marketing authorisation.

## **7 Related guidance**

7.1 NICE is in the process of producing the following clinical guideline.

Stroke: The diagnosis and acute management of stroke and transient ischaemic attacks (publication expected July, 2008).

## **8 Review of guidance**

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in April 2010.

Jonathan Michaels

Chair, Appraisal Committee

April 2007

## **Appendix A. Appraisal Committee members and NICE project team**

### **A. Appraisal Committee members**

The Appraisal Committee is a standing advisory committee of the Institute. 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice chair and a number of other members attending meetings of all branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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.

#### **Professor David Barnett**

Professor of Clinical Pharmacology, University of Leicester

#### **Dr David W Black**

Director of Public Health, Derbyshire County PCT

#### **Mr Brian Buckley**

Chairman, Incontact

#### **Dr Carol Campbell**

Senior Lecturer, University of Teesside

#### **Professor Mike Campbell**

Professor of Medical Statistics, University of Sheffield

**Professor David Chadwick**

Professor of Neurology, Liverpool University

**Dr Peter Clarke**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology,  
Merseyside

**Mr Richard Devereaux-Phillips**

Public Affairs Manager, Medtronic

**Dr Rachel A Elliott**

Clinical Senior Lecturer, University of Manchester

**Mrs Eleanor Grey**

Lay member

**Dr Dyfrig Hughes**

Senior Research Fellow in Pharmacoeconomics, Centre for the Economics of  
Health and Policy in Health, University of Wales

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Professor Peter Jones**

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele  
University

**Ms Rachel Lewis**

Practice Development Facilitator, Manchester PCT

**Dr Damien Longson**

Consultant in Liaison Psychiatry, Manchester Mental Health & Social Care  
Trust

**Professor Jonathan Michaels**

Chair of Appraisal Committee C

**Dr Eugene Milne**

Deputy Medical Director, North East Strategic Health Authority

**Dr Simon Mitchell**

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

**Dr Katherine Payne**

Health Economics Research Fellow, University of Manchester

**Dr Martin J Price**

Head of Outcomes Research, Janssen-Cilag

**Professor Andrew Stevens**

Professor of Public Health, University of Birmingham

**Dr Cathryn Thomas**

Senior Lecturer, University of Birmingham

The following individuals, representing the National Collaborating Centre responsible for developing the Institute's clinical guideline related to this topic, attended the meeting to observe and to contribute as advisors to the Committee.

- Dr Pippa Tyrell, Consultant Stroke Physician/Senior lecturer, Acute Stroke Guideline Development Group

## **B. NICE project team**

Each appraisal of a technology is assigned to one or more health technology analysts and a technology appraisal project manager within the Institute.

**Rodrigo Refoios Camejo**

Technical Lead, NICE project team

**Helen Chung**

Technical Adviser, NICE project team

**Chris Feinmann**

Project Manager, NICE project team

## Appendix B. Sources of evidence considered by the Committee

A The following manufacturer/sponsor provided a submission for this appraisal.

Boehringer Ingelheim Ltd

B The evidence review group report for this appraisal was prepared by School of Health and Related Research (SchARR), The University of Sheffield:

Lloyd Jones, M; Holmes, M. Alteplase for the treatment of acute ischaemic stroke: A Single Technology Appraisal. February 2007

C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on alteplase by providing written and oral evidence to the Committee. They were also invited to comment on the Appraisal Consultation Document (ACD).

- Professor Kennedy Lees, Associate Director, ACUTE, nominated by the Safe Implementation of Thrombolysis in Stoke (UK) Group – clinical specialist
- Professor Gary Ford, Director of, and nominated by, UK Stroke Network – clinical specialist
- Mr Peter Diamond, nominated by the British Cardiovascular Society – patient expert
- Mr Joe Korner, Director of Communications of, and nominated by, The Stroke Association – patient expert

D The following organisations accepted the invitation to participate in this appraisal. They are also provided with the opportunity to appeal against the FAD:

I Professional/specialist and patient/carer groups:

- Association of British Neurologists
- British Geriatrics Society
- British Society for Haematology
- British Society for Haemostasis and Thrombosis
- College of Emergency Medicine
- Department of Health
- Primary Care Neurology Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians (Cardiology Committee & Intercollegiate Stroke Working Party)
- South Asian Health Foundation
- Stroke Association
- UK Clinical Pharmacy Association
- Welsh Assembly Government

II Commentator organisations (without the right of appeal):

- All Wales Stroke Special Interest Group
- Centre for Health Economics, University of York and the Regional Drug and Therapeutics Centre, Newcastle
- Cochrane Stroke Group
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Collaborating Centre for Acute Care
- National Collaborating Centre for Chronic Conditions

- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Scottish Medicines Consortium
- UK Safe Implementation for Thrombolysis Study (SITS)
- UK Stroke Research Network