Complete Summary

GUIDELINE TITLE

Alteplase for the treatment of acute ischaemic stroke.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Alteplase for the treatment of acute ischaemic stroke. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jun. 22 p. (Technology appraisal guidance; no. 122).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Acute ischemic stroke

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Internal Medicine
Neurology

INTENDED USERS

Advanced Practice Nurses
Emergency Medical Technicians/Paramedics
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost-effectiveness of alteplase for the treatment of acute ischemic stroke

TARGET POPULATION

Adult patients with acute ischemic

INTERVENTIONS AND PRACTICES CONSIDERED

Alteplase (Actilyse)

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Disability
    - Proportion of patients making a good functional recovery by 3 to 6 months after treatment
    - Neurological deficit
    - Mental health including anxiety and depression
    - Survival
    - Length of hospital stay
    - Adverse events of treatment including bleeding events
    - Health-related quality of life
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), the University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description of Manufacturer's Search Strategy and Comment on whether the Search Strategy Was Appropriate

The searches undertaken by the manufacturer to identify relevant clinical trials were conducted in September 2006, using search strategies which were noticeably simpler than those used in the Cochrane review. They obviously differed from the latter inasmuch as they were intended only to identify studies of alteplase, not all thrombolytic drugs. However, they also differed in that they were designed to be considerably less sensitive in identifying either randomised controlled trials or studies relating to stroke. Consequently, whilst the manufacturer's Medline search strategy identified the key publication relating to each of the included trials, it did not identify the important reanalysis of the NINDS study, two supplementary analyses which the submission identified as relevant, or the Cochrane review on which the submission draws heavily.

The submission also draws on evidence from a number of observational studies. It is not clear how these studies were identified. Supplementary data provided by the manufacturer stated that a systematic search was undertaken for these, but did not provide a relevant search strategy. The main submission implies that the same search strategies were used to identify both clinical trials and studies investigating or evaluating service delivery or provision of technology. However, both the Embase and Medline searches contained a term limiting the search to clinical trials, and therefore neither would identify observational studies. It has not been possible, within the time available, for the ERG to conduct supplementary searches to ensure that relevant studies were not missed as a consequence.

The publicly available databases searched by the manufacturer were Medline, Embase, EBM reviews, and the Cochrane database of systematic reviews; the Cochrane Central Register of Controlled Trials does not seem to have been searched. Language restrictions do not appear to have been applied.

Statement of the Inclusion/Exclusion Criteria Used in the Study Selection and Comment on whether They Were Appropriate

The inclusion/exclusion criteria used in selecting studies of clinical effectiveness are not set out clearly in any one place. The manufacturer's submission states that the inclusion criteria were as follows:

- Randomized controlled trials (RCTs) of alteplase in acute ischaemic stroke
- Large observational cohort studies of thrombolysis in acute ischaemic stroke
- Evaluation studies of service delivery of thrombolysis in acute ischaemic stroke
- Any United Kingdom (UK)-based thrombolysis study (by which is presumably meant any UK-based study of thrombolysis for acute ischaemic stroke).

It is further specifies that the searches sought to identify:

- RCTs which randomised more than 50 patients

- Reviews, editorials, and "studies investigating/evaluating service delivery/provision of the technology"
- Any study undertaken in the UK in relation to the technology.

The exclusion of RCTs simply because they randomised fewer than 50 patients is an arbitrary criterion, which requires further explanation.

The manufacturer's submission clarifies that studies of alteplase given intra-arterially were excluded, since this is not a licensed form of administration. However, no exclusion criteria were applied to exclude studies which used intravenous alteplase at an unlicensed dose, or outside the licensed time-window.

The inclusion and exclusion criteria for the observational studies are summarised in Table 2 of the Assessment Report (see the "Availability of Companion Documents" field).

Refer to Section 4.1.3 and 4.1.4 of the ERG Report (see "Availability of Companion Documents" field) for more information.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

The manufacturer's submission identified 6 randomised controlled trials (RCTs) and seven observational studies. Two additional observational studies were identified by the Evidence Review Group (ERG).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the School of Health and Related Research (ScHARR), the University of Sheffield (see the "Availability of Companion Documents" field).

The critical appraisal of study quality and generalisability of included RCTs is provided in Table 8 of the Assessment Report (see the "Availability of Companion Documents" field).

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 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).

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.

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. The 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.

Refer to Section 3 of the original guideline document and Sections 4.1 and 4.2 of the ERG Report (see the "Availability of Companion Documents" field) for detailed discussion of methods used to analyze the evidence.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

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.

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 odds ratios (ORs) for the three health states in patients treated with alteplase were based on the Cochrane Review's meta-analysis of alteplase randomized controlled trials (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.

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 pounds sterling 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 pounds sterling/QALY gained.

The Evidence Review Group (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 relative risk (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.

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.

Refer to Sections 4.5, 4.6, and 4.7 of the original guideline document for additional information on cost-effectiveness.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of alteplase for the treatment of acute ischemic stroke

POTENTIAL HARMS

Intracranial haemorrhage is the most significant adverse event associated with alteplase.

For full details of side effects and contraindications, see the summary of product characteristics (SPC) available at http://emc.medicines.org.uk/.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (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 National Institute for Health and Clinical Excellence (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.
- "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.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA122) (see also the "Availability of Companion Documents" field).
    - Local costing template incorporating a costing report to estimate the savings and costs associated with implementation.
    - Audit criteria to monitor local practice.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Alteplase for the treatment of acute ischaemic stroke. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jun. 22 p. (Technology appraisal guidance; no. 122).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jun

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: 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 and 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

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Alteplase for the treatment of acute ischaemic stroke. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jun. 2 p. (Technology appraisal 122). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Costing template and report: alteplase for the treatment of acute ischaemic stroke. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jun. Various p. (Technology appraisal 122). Available in Portable Document Format (PDF) from the NICE Web site.
- Alteplase for the treatment of acute ischaemic stroke. Audit criteria. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jun. 11 p. (Technology appraisal 122). Available in Portable Document Format (PDF) from the NICE Web site.
- Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal. Evidence Review Group Report. School of Health and Related Research (ScHARR), The University of Sheffield, UK. 2007 Feb 7. 81 p. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1276. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Alteplase for the treatment of acute ischaemic stroke. Understanding NICE guidance - Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Jun. 4 p. (Technology appraisal 122).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1277. 11 Strand, London, WC2N 5HR.

them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI Institute on August 6, 2007.

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