

alteplase, 10mg, 20mg, 50mg, powder and solvent for solution for injection and infusion (Actilyse®) SMC No. (714/11)

Boehringer Ingelheim

10 June 2011 (*Issued 04 May 2012*)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

alteplase (Actilyse®) is accepted for use within NHS Scotland.

Indication under review: the fibrinolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible within 4.5 hours after onset of the stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage).

Evidence for the extension of the time window in which alteplase can be administered is from a placebo-controlled study. Alteplase treatment resulted in significantly more patients having no symptoms or no significant disabling symptoms at three months compared to placebo.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For the fibrinolytic treatment of acute ischaemic stroke, treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

Dosing Information

The recommended dose is 0.9mg 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.

Treatment must be prescribed by a physician trained and experienced in neurovascular care.

Product availability date

10 April 2012

Summary of evidence on comparative efficacy

Alteplase is a recombinant antithrombotic agent that activates plasminogen, converting it to plasmin. Plasmin degrades fibrin, leading to the dissolution of clots. Alteplase has previously been accepted by the Scottish Medicines Consortium (SMC) for the treatment of acute ischaemic stroke when administered within a treatment time window of three hours from the onset of symptoms. The indication under review relates to an extension to the licence, increasing the treatment time window in which alteplase can be administered, from three to 4.5 hours after the onset of stroke symptoms.

Evidence presented for the use of alteplase in the indication under review was taken from a randomised, double-blind, placebo-controlled study, and supported by data from a retrospective cohort study.

The pivotal study recruited patients aged between 18 and 80 years presenting with acute ischaemic stroke and who had onset of stroke symptoms three to 4.5 hours before initiation of study-drug treatment. Patients were randomised to receive either placebo (n=403) or alteplase (n=418) intravenously at a dose of 0.9mg/kg, up to a maximum of 90mg. The primary outcome was disability at three months assessed using the modified Rankin Scale. This is a seven-point functionality scale from zero to six in which a score of zero is allocated to a patient with no symptoms and a score of six to patient death. Scores between one and five are allocated to no significant disabling symptoms, slight disability, moderate disability, moderate to severe disability and severe disability requiring constant nursing care. A score of either zero or one was categorised as a favourable outcome and a score of two to six was categorised as an unfavourable outcome. A non-favourable outcome was attributed to those with missing data.

Patients treated with alteplase were significantly more likely to have a favourable outcome at three months in comparison to patients treated with placebo, with an adjusted odds ratio of 1.42

(95% confidence interval [CI]: 1.02 to 1.98). A favourable outcome was reported in 52% (n=219/418) of patients in the alteplase group, compared to 45% (n=182/403) of patients given placebo, an absolute difference of 7.2%.

As a secondary outcome, patients were also assessed using neurological and other functional tools. The Barthel Index assesses ability to perform activities of daily living on a scale of 0 (complete dependence) to 100 (independence), with a favourable outcome defined as a score ≥ 95 in this study; the Glasgow Outcome Scale assesses disability, with a favourable outcome defined as a score of 1 (independence). The National Institute for Health Stroke Scale assesses neurological impairment, and a favourable outcome was defined as a score of 0 or 1. A global outcome measure combined the outcomes from these tools and the modified Rankin Scale, resulting in an estimated odds-ratio of a favourable outcome of 1.28 (95% CI: 1.00 to 1.65) for alteplase over placebo.

In support of the results of the pivotal study, a retrospective cohort study presented observational data from a total of 12,529 patients from the Safe Implementation of Treatments in Stroke – International Stroke Thrombolysis Registry. Patients were divided into two groups: those who had been treated within three hours (n=11,865); and those treated between three and 4.5 hours (n=664). Recovery following treatment was evaluated using the modified Rankin Scale at three months. There was no difference between the groups in the rate of excellent recovery, defined as a score of zero or one (odds ratio 1.01 [95% CI: 0.93 to 1.10]), or in functional independence, defined as a score of zero to two (adjusted odds ratio 0.93 [95% CI: 0.84 to 1.03]).

Summary of evidence on comparative safety

Safety endpoints in the pivotal study included mortality at 90 days, incidence of intracranial haemorrhage, symptomatic intracranial haemorrhage and symptomatic oedema.

An intracranial haemorrhage was diagnosed in 27% (n=113/418) of patients treated with alteplase and in 18% (n=71/403) of patients treated with placebo. There was a significant difference between the groups and the calculated odds ratio indicated that patients treated with alteplase were 1.73 (95% CI: 1.24 to 2.42) times more likely to develop an intracranial haemorrhage. All symptomatic haemorrhages diagnosed in the study occurred in the first 22 to 36 hours after commencement of treatment. Patients treated with alteplase were more likely to develop a symptomatic intracranial haemorrhage (2.4%, n=10/418) compared to those given placebo (0.3%, n=1/403), with an estimated odds ratio of 9.85 (95% CI: 1.26 to 77.32). There was no difference between the groups for the incidence of symptomatic oedema: alteplase (6.9%, n=29/418) compared with placebo (7.2%, n=29/403), with an odds ratio of 0.96 (95% CI: 0.56 to 1.64). There was no significant difference between the groups in mortality rate: alteplase (7.7%, n=32/418) compared with placebo (8.4%, n=34/403) with an odds ratio of death of 0.9 (95% CI: 0.54 to 1.49).

The retrospective cohort study noted no significant differences in the rates of intracranial haemorrhages or mortality at three months between those treated within three hours or those treated between three and 4.5 hours of symptom onset.

Summary of clinical effectiveness issues

Alteplase is the only thrombolytic medicine licensed in the UK for use in the management of acute ischaemic stroke.

There were some differences in the baseline characteristics of the two groups randomised to alteplase or placebo in the European Cooperative Acute Stroke Study (ECASS) III study, which may have confounded the results: past history of stroke (7.7% versus 14% respectively), and baseline National Institute of Health Stroke Scale (NIHSS, a 42-point scale in which higher scores relate to greater degrees of neurological impairment) score (10.7/42 versus 11.6/42 respectively). The statistical analysis of the study accounted for the difference in NIHSS score, as the estimated odds ratio of the primary endpoint was adjusted for this factor as well as the time to commencement of treatment.

Alteplase has been recommended for use in acute ischaemic stroke up to 4.5 hours post onset of symptoms in guidelines prepared by the Scottish Intercollegiate Guidelines Network (SIGN) and the European Stroke Organisation. Both guidelines note that treatment benefit is strongly related to the time to treatment and is significantly greater the earlier the treatment is delivered.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing alteplase with placebo in the setting of the extended licence i.e. patients 3- 4.5 hours after an ischaemic stroke. The analysis was based on a state transition decision analytic model that had previously been used in a submission to the National Institute for Health and Clinical Excellence (NICE) and classed patients as 'independent', 'dependent' or 'dead'.

The model consisted of three stages:

- The treatment phase (from 0-6 months) where the 'usual care' arm outcomes were taken from published analysis of the Lothian Stroke Registry. These outcomes were then adjusted according to the results of the pivotal clinical study supporting the licence extension.
- The post-treatment phase (from 6-12 months) where the transition probabilities were taken solely from the published analysis of the Lothian Stroke Registry.
- The extension phase (beyond 12 months) where mortality rates were applied based on age-adjusted population levels taking account of excess risk as a result of history of stroke.

Costs included the medicine itself but an important element was the NHS staff time to administer and monitor treatment; assumptions were based on a previous health technology appraisal (HTA) report on this topic. Costs of ongoing care were based on a second published study of the 12-month NHS and social service costs following stroke at different levels of severity and of a death resulting from stroke. These were adapted and updated using the PSSRU inflation index for NHS costs.

Utilities for the health states 'independent' and 'dependent' were taken from the published HTA report analysing EQ-5D data from patients on the Lothian Stroke Registry.

The results showed the addition of alteplase costs an extra £1,391 over the patient's lifetime (£26,785 versus £25,394) and yielded an extra 0.32 quality adjusted life years (QALYs) (2.98 versus 2.67). This gave an incremental cost per QALY of £4,384.

Sensitivity analysis was provided with higher cost per QALY figures resulting from the following scenarios:

- On one-way analysis when the effects of alteplase on either dependency or on death were excluded (£8,679 per QALY and £8,001 per QALY respectively)
- On two-way sensitivity analysis if the effect of alteplase on death were excluded and staff costs of administering the medicine were doubled then the cost per QALY rose to £19,006.

Whilst there are potentially higher cost-effectiveness ratios shown in the sensitivity analysis, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published guidance on “Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention” in December 2008. This recommends that patients admitted within 4.5 hours of definite onset of symptoms who are considered suitable should be treated with intravenous alteplase at a dose of 0.9mg/kg, up to a maximum of 90mg.

The National Institute for Clinical Excellence published a clinical guideline “Stroke: Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)” in July 2008. It recommends alteplase for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke and that it should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation.

The European Stroke Organisation updated “Guidelines for the management of ischaemic stroke and transient ischaemic attack” in 2009 which recommends that intravenous alteplase is administered within 4.5 hours of onset of ischaemic stroke, while acknowledging that treatment between three and 4.5 hours is out-with the European labeling.

Additional information: comparators

There are no comparator treatments for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Alteplase	0.9mg/kg intravenously, to a maximum 90mg	480

Cost taken from the Monthly Index of Medical Specialities (February 2011) and is based on a body weight of 70kg (dose of 63mg)

Additional information: budget impact

The manufacturer estimated there would be 181 additional eligible patients per annum based on a 2002 survey of the distribution of stroke patients in terms of time from onset of symptoms to arrival at hospital. An allowance was made of 69 minutes as the average “door-to-needle” time for thrombolysis in the UK. Full market share was assumed. While this is high, clinical experts consulted by SMC make clear that they use thrombolysis wherever possible so the estimate is broadly plausible. The net impact on the medicines budget impact was estimated at £87k per annum. Clinical experts have indicated that alteplase use up to 4.5 hours has already been implemented following the publication of the trial results and changes to the SIGN guidelines in 2008 so the additional budget impact would be minimal.

References

The undernoted references were supplied with the submission.

Hacke W, Kaste M, Bluhmki E et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. New England Journal of Medicine (2008); 359 (13): 1317-29.

Sandercock P, Berge E, Dennis, et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Health Technol Assess (2002); 6 (26).

Wahlgren N, Ahmed N, Davalos A et al. Thrombolysis with alteplase 3-4.5h after acute ischaemic stroke (SITS-ISTR): an observational study. The Lancet (2008); 372: 1303-9.

Youman P, Wilson K, Harraf F et al. The economic burden of stroke in the United Kingdom. Pharmacoeconomics (2003); 21 (suppl. 1): 43-50.

This assessment is based on data submitted by the applicant company up to and including 12 April 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.