National Institute for Health and Clinical Excellence

SingleTechnology Appraisal (STA)

Alteplase for the treatment of acute ischaemic stroke (review of technology appraisal 122)

Response to consultee and commentator comments on the draft scope (pre-referral)

Comment: the draft scope

Section	Consultees	Comments	Action
Background information	British Association of Stroke Physicians	Satisfactory	Comment noted.
	British Hypertension Society	Adequate	Comment noted.
	Association of British Neurologists	Satisfactory	Comment noted.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	Background information describes all causes of stroke (ischaemic and haemorrhagic) and mentions thrombolysis without stipulating that this is for ischaemic stroke only. It would be better to emphasise in this first sentence that thrombolysis is for ischaemic stroke only.	Comment noted. The background is intended to only provide a brief overview of the condition. A more detailed explanation will be included in the manufacturer's submission. Paragraph one in the background section states that "an ischaemic stroke arises when there is a blockage in a blood vessel serving the brain caused by a blood clot (thrombus)".
	IST3 Trial Group, University of Edinburgh	Satisfactory	Comment noted.
The technology/ intervention	British Association of Stroke Physicians	Yes	Comment noted.
	British Hypertension Society	Yes	Comment noted.

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	Boehringer Ingelheim	We would recommend that the scope of the appraisal is limited to 3-4.5 hours window since the appraisal of the 0-3 hours window is adequately covered by technology appraisal 122 (June 2007) and no relevant new evidence is now available which was not available to that appraisal. We would recommend that the results of the appraisal covered by this scope incorporate the TA122 June 2007 recommendation into a single guidance covering the 0-4.5 hours window use of alteplase. A further reason for arguing that the 3-4.5 hours window is analysed separately is that this is aligned to the relevant clinical trial (ECASS III) inclusion criteria for which was onset of stroke symptoms of 3-4.5 hours.	Comment noted. Because the proposed appraisal is a review of existing technology appraisal 122, it is necessary that this appraisal will consider both the existing available evidence related to the 0-3 hours window along with any new evidence related to the 3-4.5 hours window. This will ensure that alteplase is appraised within its licensed indication for acute ischaemic stroke. The resulting guidance will replace existing recommendations in TA122.
	Association of British Neurologists	Yes	Comment noted.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	"The aim of the treatment is to reduce the impact of the ischaemia by degrading the blood clot that caused the ischaemia". I think better to say "the aim of the treatment is to reduce ischaemia by restoring blood flow through the occluded (or blocked) artery". You can't reduce the impact of ischaemia with thrombolysis. You restore blood flow to reduce brain damage.	Comment noted. The relevant sentence has been changed to: "The aim of treatment is to reduce the impact of ischaemia by restoring blood flow through the occluded (or blocked) artery".
	IST3 Trial Group, University of Edinburgh	Yes	Comment noted.
Population	British Association of Stroke Physicians	No. There are groups of ischaemic stroke patients in whom the benefit of alteplase is possible, but currently uncertain or not recommended in the current license. These groups include individuals over the age of 80 years, beyond 3 hours of stroke onset; those with	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.

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		minor or resolving deficits; and those with previous stroke and diabetes mellitus. A large scale randomized trial, IST-3, co-ordinated from Edinburgh University, will provide important information on these aspects in May 2012 (see below).	
	British Hypertension Society	There needs to be consideration of those currently not within the current licence eg 80+ age group where new data may be available.	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.
	Association of British Neurologists	No. There are groups of ischaemic stroke patients in whom the benefit of alteplase is possible, but currently uncertain or not recommended in the current license. These groups include individuals over the age of 80 years, beyond 3 hours of stroke onset; those with minor or resolving deficits; and those with previous stroke and diabetes mellitus. A large scale randomized trial, IST-3, co-ordinated from Edinburgh University, will provide important information on these aspects in May 2012 (see below).	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	The current license is up to 80 years. The IST-3 study will be published in May 2012 which will review data on up to 6 hours and people over the age of 80. I would therefore include over 80s and up to 6 hours. You will need to contact the IST-3 investigators so you can have access to this data prior to undertaking the assessment. If you don't include IST-3 you will only have RCT data for people up to the age of 80 unless you include post marketing data eg SITS-MOST.	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.
	IST3 Trial Group, University of Edinburgh	No. Patients aged over 80, and other categories patients with relative contraindications to thrombolysis according to the current marketing authorisation (eg patients with a combination of diabetes mellitus and	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.

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		prior stroke).	
Comparators	British Association of Stroke Physicians	Yes	Comment noted.
	British Hypertension Society	Yes	Comment noted.
	Association of British Neurologists	Yes	Comment noted.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	Yes, but thrombolysis is standard treatment now so difficult to compare as the population in the comparator will be very different from the placebo or control trial populations. There is no clinical equipoise except for people over 80 and thrombolysis between 4.5 and 6 hours.	Comment noted. In the previous technology appraisal of alteplase for the treatment of acute ischaemic stroke (TA 122) it was acknowledged by the Committee that the clinical locations in which the RCTs were run enabled both patients who were treated with alteplase and those who received placebo access to the same quality of care, which included prompt assessment, supportive management and careful monitoring. In the absence of any other active treatments that are currently available for acute ischaemic stroke, it is agreed that standard medical and supportive management that does not include alteplase would be the appropriate comparator for this appraisal.
	IST3 Trial Group, University of Edinburgh	Yes	Comment noted.
Outcomes	British Association of Stroke Physicians	Yes. Within the outcome category of bleeding events, cerebral haemorrhage should be considered separately as it is the most serious complication of this treatment.	Comment noted. Cerebral haemorrhage is covered under the outcome category of adverse effects of treatment, including bleeding events.
	British Hypertension	Yes	Comment noted.

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	Society		
	Association of British Neurologists	Yes. Within the outcome category of bleeding events, cerebral haemorrhage should be considered separately as it is the most serious complication of this treatment.	Comment noted. Cerebral haemorrhage is covered under the outcome category of adverse effects of treatment, including bleeding events.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	There is no trial data on changes in mental health, health related QoL or LOS. You therefore won't be able to assess these. Bleeding events are important but specifically differentiate symptomatic intracerebral haemorrhage, asymptomatic ICH, extracranial bleeding. Angio-oedema is an increasingly recognised complication.	Comment noted. Bleeding events and angio-oedema are covered under the outcome category of adverse effects of treatment, including bleeding events.
	IST3 Trial Group, University of Edinburgh	Yes	Comment noted.
Economic analysis	British Association of Stroke Physicians	No comment	Comment noted.
	Boehringer Ingelheim	See the answer under the technology / intervention	Comment noted.
	Association of British Neurologists	No comment	Comment noted.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	Difficult to know where this data will come from unless it is data supplied by the manufacturer. I do not know of trial data that includes this.	Comment noted. As this is an STA, the evidence submission will be developed by the manufacturer of alteplase.
Equality and Diversity	British Association of Stroke Physicians	No comment	Comment noted.
	British Hypertension	As above all age groups need to be considered where	Comment noted. NICE can only appraise

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	Society	new data may be available.	alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.
	Association of British Neurologists	No comment	Comment noted.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	Age is an important issue and this is another reason why you need to include the IST-3 results which will definitively inform use of the technology in people > 80	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.
Innovation	Boehringer Ingelheim	There is substantial evidence that access to alteplase is hampered by patients not getting to hospital and receiving a CT scan within 3 hours. Extending the window for use to 4.5 hours would be anticipated to improve access.	Comment noted.
Other considerations	British Association of Stroke Physicians	There is a need to predict those individuals at risk of serious bleeding, especially cerebral haemorrhage. Further research into this aspect (including risk models incorporating neuroimaging methods) should be strongly encouraged. There is increasing interest in combining the use of alteplase with endovascular techniques including intra-arterial administration with or without mechanical clot extraction. This should perhaps be mentioned but detailed consideration is beyond the scope of the proposed appraisal.	Comments noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke within its licensed indication.
	British Hypertension Society	Data from the IST3 trial should be considered where important information on the 80+ age group and an extended time window for treatment (ie up to 4.5 hours) will be available. It would be a missed opportunity if these data, which I believe will shortly (in	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.

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		the next 4-5 months) be available, are not considered.	
	Association of British Neurologists	There is a need to predict those individuals at risk of serious bleeding, especially cerebral haemorrhage. Further research into this aspect (including risk models incorporating neuroimaging methods) should be strongly encouraged. There is increasing interest in combining the use of alteplase with endovascular techniques including intra-arterial administration with or without mechanical clot extraction. This should perhaps be mentioned but detailed consideration is beyond the scope of the proposed appraisal.	Comments noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke within its licensed indication.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	Add 4.5 to 6 hours	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke within the time window specified in its UK marketing authorisation.
	IST3 Trial Group, University of Edinburgh	Appraisal should take into account the data from the large scale IST3 randomised trial, which has included 3035 patients, 1617 of whom were aged over 80. The trial also provides additional information on individuals covered both by the current, and proposed extension to the marketing authorisation; 849 patients treated within 3 hours, 1178 treated 3-4.5 hrs after onset. These data will be presented at ESC on 23rd May 2012 and published simultaneously in the Lancet	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation.
Questions for consultation	British Association of Stroke Physicians	Yes. No. Data is available from large scale randomized trials.	Comment noted.
	British Hypertension Society	Yes	Comment noted.

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	Association of British Neurologists	Yes. No. Data is available from large scale randomized trials.	Comment noted.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	How should standard management be defined? This question was answered by the IST-3 team who developed criteria for standard management which was the control arm of IST-3. I would suggest talking to them. However, in the absence of clinical equipoise for up to 4.5 hours and <80 any comparator will not include patients matched to the intervention group: they will be patients who for whatever reason did not fulfil criteria for thrombolysis. The only "true" comparator would be patients who are eligible for thrombolysis but did not receive it because they were admitted to a hospital that does not provide it. However there is no data on these people.	Comment noted. In the previous technology appraisal of alteplase for the treatment of acute ischaemic stroke (TA 122) it was acknowledged by the Committee that the clinical locations in which the RCTs were run enabled both patients who were treated with alteplase and those who received placebo access to the same quality of care, which included prompt assessment, supportive management and careful monitoring. In the absence of any other active treatments that are currently available for acute ischaemic stroke, it is agreed that standard medical and supportive management that does not include alteplase would be the appropriate comparator for this appraisal.
Additional comments on the draft scope.	British Association of Stroke Physicians	Appraisal should take into account the data from the large scale IST-3 randomised trial, which has included 3035 patients, 1617 of whom were aged over 80. The trial also provides additional information on individuals covered both by the current, and proposed extension to the marketing authorisation; 849 patients treated within 3 hours, 1178 treated 3-4.5 hrs after onset. These data will be presented at European Stroke Conference on 23rd May 2012 and published simultaneously in the Lancet. Should the appraisal await data from IST-3?	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation. In order to produce timely guidance within 6 months of the extension to the marketing authorisation being granted, it is important that this topic is scheduled into the work programme as soon as possible. The manufacturer of alteplase will be responsible for preparing the evidence submission for this appraisal. Unpublished results from the IST-3 trial can be included at the manufacturer's discretion.
	British Hypertension Society	It would be inappropriate for the Appraisal to go ahead until data from IST3 are available.	Comment noted. In order to produce timely guidance within 6 months of the extension to the

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			marketing authorisation being granted, it is important that this topic is scheduled into the work programme as soon as possible. The manufacturer of alteplase will be responsible for preparing the evidence submission for this appraisal. Unpublished results from the IST-3 trial can be included at the manufacturer's discretion.
	Association of British Neurologists	Appraisal should take into account the data from the large scale IST-3 randomised trial, which has included 3035 patients, 1617 of whom were aged over 80. The trial also provides additional information on individuals covered both by the current, and proposed extension to the marketing authorisation; 849 patients treated within 3 hours, 1178 treated 3-4.5 hrs after onset. These data will be presented at European Stroke Conference on 23rd May 2012 and published simultaneously in the Lancet. Should the appraisal await data from IST-3?	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation. In order to produce timely guidance within 6 months of the extension to the marketing authorisation being granted, it is important that this topic is scheduled into the work programme as soon as possible. The manufacturer of alteplase will be responsible for preparing the evidence submission for this appraisal. Unpublished results from the IST-3 trial can be included at the manufacturer's discretion.
	ScHARR-TAG	It is expected that a subgroup analysis of males and females will be necessary.	Comment noted. In the previous technology appraisal of alteplase for the treatment of acute ischaemic stroke (TA 122) any differences in clinical or cost effectiveness of alteplase according to gender were not considered or discussed by the Committee.
	National Clinical Guideline Centre (on behalf of the Acute Stroke and TIA 2008 GDG)	The technology is now standard practice across the UK and strenuous efforts have been made to increase the availability of this technology to the people who need it. There is no equipoise clinically for its use in people under 80 within 4.5 hours who fulfll appropriate clinical criteria (eg no haemorrhage on CT scan, no history of ICH, no active bleeding, no history suggestive of SAH, no coagulopathy, definite time of	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population time window indicated in its UK marketing authorisation.

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		onset,) and who are being managed by staff trained and experienced in its use in stroke units where the staff are trained in the management of complications. There is equipoise for patients > 80 and 4.5 to 6 hours. IST-3 data is therefore essential.	
	IST3 Trial Group, University of Edinburgh	Appraisal should take into account the data from the large scale IST3 randomised trial, which has included 3035 patients, 1617 of whom were aged over 80. The trial also provides additional information on individuals covered both by the current, and proposed extension to the marketing authorisation; 849 patients treated within 3 hours, 1178 treated 3-4.5 hrs after onset. These data will be presented at ESC on 23rd May 2012 and published simultaneously in the Lancet. It would seem sensible to delay the appraisal until after those data are available! See attached draft manuscript which provides additional information on the patients included in the IST3 trial. This paper will be published in the journal *Trials* (www.trialsjournal.com) on 30.11.11	Comment noted. NICE can only appraise alteplase for the treatment of acute ischaemic stroke for the population indicated in its UK marketing authorisation. In order to produce timely guidance within 6 months of the extension to the marketing authorisation being granted, it is important that this topic is scheduled into the work programme as soon as possible. The manufacturer of alteplase will be responsible for preparing the evidence submission for this appraisal. Unpublished results from the IST-3 trial can be included at the manufacturer's discretion.

The following consultees/commentators indicated that they had no comments on the draft scope

- Department of Health
- Royal College of Nursing
- Royal College of Physicians