National Institute for Health and Care Excellence

Health Technology Evaluation

Tenecteplase for treating acute ischaemic stroke [ID6306]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Boehringer Ingelheim	BI agree that the evaluation of this topic and the Single Technology Appraisal route are appropriate to evaluate the clinical and cost effectiveness of tenecteplase (to be administered at a dose of 0.25 mg/kg to a maximum of 25 mg).	Thank you for your comment. Following the scoping exercise, this topic has been routed to a cost comparison appraisal.
	British and Irish Association of Stroke Physicians	None	No action required.
Wording	Boehringer Ingelheim	The wording is not consistent with the proposed marketing authorization. Please use the term 'fibrinolytic' in place of 'thrombolytic'. The remit should therefore read: 'To appraise the clinical and cost effectiveness of tenecteplase within its marketing authorisation for the fibrinolytic treatment of acute ischaemic stroke'.	Comment noted. The title of the topic has been updated to align with TA264. The remit of the topic has been aligned with the

Section	Stakeholder	Comments [sic]	Action
			proposed marketing authorisation wording suggested.
	British and Irish Association of Stroke Physicians	None	No action required.
Timing Issues	Boehringer Ingelheim	Intravenous thrombolysis with alteplase is the standard treatment in AIS, and currently 10.7% of all stroke patients in England, Wales and Northern Ireland receive thrombolysis [6]. Alteplase has been recommended by NICE in 2012 [1], but a high unmet need remains in the AIS population to prevent disabilities and deaths. Firstly, the administration of alteplase is complex and time consuming, as it requires a two-sequence administration as a bolus plus infusion over 60 minutes. A thrombolytic with a simpler and quicker route of administration could improve patient management and reduce healthcare costs. Consequently, since 2019, there has been a growing trend towards the off-label use of tenecteplase in AIS, driven by the publication of independent academic clinical research and subsequent recommendations in major stroke guidelines [2] [3] [4] [5]. There is now a large body of evidence supporting the use of tenecteplase for the treatment of AIS including RCTs, meta-analyses, and real-world studies (please see the details in the *Questions for Consultation* section). Tenecteplase has improved pharmacokinetic and pharmacodynamic properties compared with alteplase, including greater fibrin specificity, greater resistance to inactivation by plasminogen activator inhibitor-1 (PAI-1), less disruption of hemostasis, and longer free plasma half-life, allowing for faster and more convenient 5–10 second single IV bolus administration, and therefore no IV pump or any specialized equipment is needed [7] [8] [9].	Comment noted. No action required. The following national guideline has been included under 'Related national policy' section: National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4. Available at: www.strokeguideline.org.

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		Secondly, there is wastage associated with unused drug when reconstituting Metalyse® 50 mg vials for use in AIS [10] [11]. Metalyse® 25 mg for AIS addresses the unmet need of easier administration, and optimal AIS-dosing pack size. Consequently, there is a need to make tenecteplase 25mg widely available in the NHS. [1] NICE (2012) Alteplase for treating acute ischaemic stroke (TA264). [Online] Accessed 19 September 2023. Available at (www.nice.org.uk/guidance/ta264) [2] National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4. Available at: www.strokeguideline.org. [3] Alamowitch S, Turc G, Palaiodimou L, Bivard A, Cameron A, De Marchis GM, et al. European Stroke Organisation (ESO) expedited recommendation on Tenecteplase for acute ischaemic stroke. Eur Stroke J. 2023 Mar;8(1):8-54 [4] Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12):e344-e418 [5] Stroke Foundation. 2022 Australian and New Zealand Living Clinical Guidelines for Stroke Management. Chapter 3 of 8: Acute medical and surgical management. Available at: https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management. Last accessed: 15 June 2023 [6] Sentinel Stroke National Audit Programme (SSNAP) Annual Portfolio for April 2022-March 2023. [7] Keyt BA, Paoni NF, Refino CJ, et al. A faster-acting and more potent form of tissue plasminogen activator. Proc Natl Acad Sci U S A. 1994;91(9):3670–3674 [8] Safouris A, Magoufis G, Tsivgoulis G. Emerging agents for the treatment and prevention of stroke: progress in clinical trials. Expert Opin Investig Drugs. 2021 Oct;30(10):1025-35 [9] 3 Singh N, Menon BK, Dmytriw AA, Regenhardt RW, Hirsch JA, Ganesh A. Replacing Alteplase with Tenecteplase: Is the Time Ripe? J Stroke. 2023 Jan;25(1):72-80 [10] Boehringer Ingelheim International GmbH. Metalyse. Summary of Product Characteristics (SPC). 23 January 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/metalyse-epar-product-information_en.pdf [11] Dittmar E, Wolfel T, Menendez L, Pozo J, Ramirez M, Belnap SC, et al. Conversion From Intravenous Alteplase to Tenecteplase for Treatment of Acute Ischemic Stroke Across a Large Community Hospital Health System. Ann Pharmacother. 2023 Jan 23:10600280221149409	

Section	Stakeholder	Comments [sic]	Action
	British and Irish Association of Stroke Physicians	None	No action required.
Additional comments on the draft remit	Boehringer Ingelheim	None	No action required.
	British and Irish Association of Stroke Physicians	None	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Boehringer Ingelheim	The background information appears to be accurate.	No action required.
	British and Irish Association of Stroke Physicians	National Stroke Service model May 2021 https://www.england.nhs.uk/wp-content/uploads/2021/05/stroke-service-model-may-2021.pdf National Stroke Clinical Guideline April 2023 https://www.strokeguideline.org/contents/ National Stroke GIRFT report April 2022 https://gettingitrightfirsttime.co.uk/medical_specialties/stroke/	Comment noted. The policies have now been added to the 'Related national policy' section of the scope.
Population	Boehringer Ingelheim	Yes, it is appropriate to define the population as 'People with acute ischemic stroke who can have thrombolytic treatment'.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	British and Irish Association of Stroke Physicians	None	No action required.
Subgroups	Boehringer Ingelheim	The evidence on efficacy and safety for this submission is based on two clinical trials, AcT [1] and EXTEND-IA TNK [3]. AcT was a pragmatic, registry linked, prospective, randomised controlled, open-label parallel group clinical trial with blinded endpoint assessment comparing tenecteplase versus alteplase in Canadian patients with AIS eligible to receive intravenous alteplase as per standard care (n=1600). The study demonstrated that in patients with AIS presenting within 4.5 hours of stroke symptom onset, tenecteplase demonstrated a clinically relevant non-inferiority to alteplase for the primary outcome of excellent functional outcome (measured as modified Rankin Scale score 0–1) at 90–120 days. The direction of the effect favoured tenecteplase, however this was not statistically significant. These results were consistent across all pre-specified subgroups including: age (<80 vs ≥80 years), sex, baseline stroke severity, symptom onset-to-needle time, large vessel occlusion, type of enrolling centre, and source registry for both ITT and per-protocol populations. There were no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage, extracranial bleeding, or 90-day mortality. A subgroup analysis of time to thrombolysis (0-3 hour versus 3-4.5-hour), showed the effect of time to tenecteplase administration on clinical outcomes is like that of alteplase with faster administration resulting in better clinical outcomes.[2] EXTEND-IA TNK was a prospective, randomized, open-label, blinded-outcome trial comparing tenecteplase with alteplase in Australian patients with ischemic stroke within 4.5 hours after onset who had large-vessel	Comment noted. Boehringer Ingelheim should note that committee may still want to see the outcomes of this analysis (time to thrombolysis (0-3 hours versus 3-4.5 hours). The technical team propose that Boehringer Ingelheim provide the clinical data to support exclusion of this subgroup analysis and/ or include this as a scenario in its submission.

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		occlusion of the internal carotid, middle cerebral, or basilar artery and who were eligible to undergo intravenous thrombolysis and endovascular thrombectomy (n=202). The study demonstrated that in patients with AIS presenting within 4.5 hours of stroke symptom onset, tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome (measured as modified Rankin Scale score at 90 days) compared to alteplase. There were no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage or 90-day mortality [3]. These findings support the recommendation of administrating tenecteplase as early as possible within 4.5 hours from last known well 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) [1] [2] [3]. Therefore, the results of tenecteplase treatment versus alteplase are applicable to the whole AIS target population, and a subgroup analysis, including the one suggested in the scope, is not justified. [1] Menon, B. K. et al. Intravenous Tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 400, 161–169 (2022). [2] Singh, N. et al. Effect of Time to Thrombolysis on Clinical Outcomes in Patients with Acute Ischemic Stroke Treated with Tenecteplase Compared to Alteplase: Analysis from the AcT Randomized Controlled Trial. Stroke 2023. Pre-published online 06 October 2023. doi: 10.1161/STROKEAHA.123.044267. [3] Campbell BCV, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med 2018; 378:1573-1582.	

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	British and Irish Association of Stroke Physicians	None	No action required.
Comparators	Boehringer Ingelheim	Alteplase is the current licensed thrombolytic treatment for AIS [1] and it is the only appropriate comparator to be considered in the appraisal of tenecteplase. In the AcT and EXTEND-IA TNK trials, alteplase was administered intravenously, with patients receiving a total dose of 0.9 mg/kg to a maximum of 90 mg. Alteplase was given as a 10% (0.09 mg/kg) bolus, followed immediately by a 60 min infusion of the remaining 90% (0.81 mg/kg) [2] [3]. This administration procedure is consistent with the posology recommended for use in the NHS, which consists of a total dose is 0.9 mg alteplase/kg body weight (maximum of 90 mg) starting with 10% of the total dose as an initial intravenous bolus, immediately followed by the remainder of the total dose infused intravenously over 60 minutes [4]. [1] NICE (2012) Alteplase for treating acute ischaemic stroke (TA264). [Online] Accessed 19 September 2023. Available at (www.nice.org.uk/guidance/ta264) [2] Menon, B. K. et al. Intravenous Tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 400, 161–169 (2022). [3] Campbell BCV, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med 2018;378:1573-1582. [4] Actilyse 10 mg powder and solvent for solution for injection and infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	Comment noted. No action required.
	British and Irish Association of	None	No action required.

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	Stroke Physicians		
Outcomes	Boehringer Ingelheim	The outcomes listed in the draft scope are appropriate and relevant.	Comment noted. No action required.
	British and Irish Association of Stroke Physicians	The reconfigurations of stroke units nationally and the location of limited number of neuroscience centres delivering thrombectomy are critical to consider in the delivery of acute reperfusion therapies. A huge consideration should be given to the shortened infusion time for single bolus Tenecteplase as compared to 1 hr infusion of alteplase. This will facilitate earlier thrombectomy and more timely ambulance transfers without the need for accompanying highly trained stroke nursing staff. This should be considered in the cost benefit analysis.	Comment noted. In the economic analysis costs will be considered from an NHS and Personal Social Services perspective. So, changes in resource use should be captured within the economic analysis. No action required.
Equality	Boehringer Ingelheim	No comment.	No action required.
	British and Irish Association of Stroke Physicians	None	No action required.
Other considerations	Boehringer Ingelheim	NICE Scope: If the evidence allows the following subgroup will be considered: subgroups by time to treatment (0 to 3 hours and 3 to 4.5 hours). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the	Comment noted. The scope specifies that if evidence allows,

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		evidence that has underpinned the marketing authorisation granted by the regulator. Boehringer Ingelheim response: The AcT and EXTEND-IA TNK trials included patients who were eligible for intravenous thrombolysis within 4.5 hrs from the onset of ischaemic stroke, consistent with the alteplase indication [1] [2]. A subgroup analysis has been conducted on the AcT trial population according to the time to thrombolysis (0-3 hours versus 3-4.5 hours). The results showed the effect of time to tenecteplase administration on clinical outcomes is similar to alteplase, with faster administration resulting in better clinical outcomes [3]. These findings support the recommendation of administrating tenecteplase as early as possible within 4.5 hours from last known well 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) [1]. The results of tenecteplase as a non-inferior treatment to alteplase are applicable to the whole AIS target population, and a subgroup analysis, including the one suggested in the scope, is not justified. It should be noted that at the time of initial alteplase appraisal, the standard practice was to administer thrombolytic treatment within the 3-hour time window. This was extended to 4.5 hours at the time of alteplase appraisal [4] and explains why these analyses were considered important at the time. This is reflected in the current stroke guidelines which recommend patients with AIS within 4.5 hours of known onset should be considered for thrombolysis [5]	consideration may be given to subgroups based on time to treatment, consistent with the appraisal of alteplase and the observed difference in clinical and cost effectiveness observed in that appraisal. If subgroups are not presented, this should be thoroughly justified.

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		[6]. We therefore believe there is no rationale for revisiting earlier versus later thrombolysis treatment windows with tenecteplase. [1] Actilyse 10 mg powder and solvent for solution for injection and infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) [2] Campbell BCV, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med 2018;378:1573-1582. [3] Singh, N. et al. Effect of Time to Thrombolysis on Clinical Outcomes in Patients with Acute Ischemic Stroke Treated with Tenecteplase Compared to Alteplase: Analysis from the AcT Randomized Controlled Trial. Stroke 2023. Pre-published online 06 October 2023. doi: 10.1161/STROKEAHA.123.044267 [4] NICE (2012) Alteplase for treating acute ischaemic stroke (TA264). [Online] Accessed 19 September 2023. Available at (www.nice.org.uk/guidance/ta264) [5] National Clinical Guideline for Stroke for the UK and Ireland. London: Intercollegiate Stroke Working Party; 2023 May 4. Available at: www.strokeguideline.org. [6] Alamowitch S, Turc G, Palaiodimou L, Bivard A, Cameron A, De Marchis GM, et al. European Stroke Organisation (ESO) expedited recommendation on Tenecteplase for acute ischaemic stroke. Eur Stroke J. 2023 Mar;8(1):8-54	
	British and Irish Association of	None	No action required.

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	Stroke Physicians		
Questions for consultation	Boehringer Ingelheim	Where do you consider tenecteplase will fit into the existing care pathway for acute ischaemic stroke? We expect tenecteplase to replace alteplase, and therefore will fit into the existing care pathway. Are all relevant comparators being considered for tenecteplase? Yes, alteplase is the only relevant comparator. Have all relevant subgroups been considered? Are there any subgroups where only alteplase can be offered as a treatment option for acute ischaemic stroke? All relevant subgroups have been investigated in the AcT trial, which demonstrated that the non-inferior efficacy of tenecteplase vs alteplase are applicable to the whole AIS target population [1] [2]. [1] Menon, B. K. et al. Intravenous Tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 400, 161–169 (2022). [2] Singh, N. et al. Effect of Time to Thrombolysis on Clinical Outcomes in Patients with Acute Ischemic Stroke Treated with Tenecteplase Compared to Alteplase: Analysis from the AcT Randomized Controlled Trial. Stroke 2023.	Comments noted. The outcomes included in the scope are non-exhaustive. Company can include additional outcomes as relevant. Following the scoping exercise, this topic has been routed to a cost comparison appraisal. Please refer to the NICE manual for inclusion of non-NHS and PSS costs (section 4.4.24) and carer quality of life (See section 4.3.17) discusses costs associated with care by family members, friends or a partner) No further action required

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		Pre-published online 06 October 2023. doi: 10.1161/STROKEAHA.123.044267 Are there any other outcomes that should be considered when evaluating the clinical and cost-effectiveness of tenecteplase? Yes, the use of endovascular thrombectomy and brain reperfusion are relevant outcomes and they may have an impact on cost-effectiveness. It is also important to consider the impact of ischemic stroke on informal caregivers. Are there any diagnostics costs (for example imaging costs) which should be considered prior to treatment with tenecteplase for acute ischaemic stroke? The use of tenecteplase will not require any additional diagnostic procedures with respect to alteplase. Diagnostic imaging of the brain through CT or other diagnostic imaging method sensitive for the presence of haemorrhage is a standard requirement to exclude intracranial haemorrhage in patients with AIS. These investigations are carried out regardless of the thrombolytic subsequently administered to AIS patients. Would tenecteplase be a candidate for managed access? No.	

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		Do you consider that the use of tenecteplase can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Not at this stage. Is tenecteplase likely to be similar in its clinical effectiveness and resource use to any of the comparators (for example, alteplase)? Or in what way is it different to the comparators? A number of studies have demonstrated that tenecteplase has similar efficacy compared to alteplase, with the direction of the effect favouring tenecteplase [1]. The safety profiles of tenecteplase and alteplase are similar [1] [2]. Regarding the use of resources, as tenecteplase has a shorter preparation and administration time versus alteplase, its administration may lead to more efficient delivery of treatment, freeing up healthcare resources, and potentially reduce time to thrombectomy in eligible patients [1]. [1] Menon, B. K. et al. Intravenous Tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 400, 161–169 (2022). [2] Campbell BCV, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med 2018;378:1573-1582.	

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		Will tenecteplase be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe It is expected that tenecteplase will be used in the same place in the treatment pathway as alteplase, and we are not aware of the introduction of any major changes at present. As tenecteplase has a shorter preparation and administration time compared to alteplase, this may lead to more efficient delivery of treatment and potentially reduce time to thrombectomy in eligible patients. Changes might also be required in consideration of the need for fewer medicalised transfer of eligible patients to thrombectomy centres and reduced nursing time. Will tenecteplase be used to treat the same population as the comparator(s)? Yes, the aim is for tenecteplase to be accessed by the same AIS population who is eligible to receive alteplase treatment. Overall is tenecteplase likely to offer similar or improved health benefits compared with the comparators? The AcT and EXTEND-IA TNK studies have demonstrated that Tenecteplase is non-inferior to alteplase in terms of efficacy, and with a similar safety profile [1] [2].	

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		[1] Menon, B. K. et al. Intravenous Tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 400, 161–169 (2022). [2] Campbell, B. C. V. et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N. Engl. J. Med. 378, 1573–1582 (2018). Would it be appropriate to use the cost-comparison methodology for this topic? We do not have at present the information and data required to decide the appropriate economic evaluation approach to address this decision problem. We will be able to provide an answer to this question in November 2023 at latest.	
	British and Irish Association of Stroke Physicians	None	No further action required
Additional comments on the draft scope	Boehringer Ingelheim	None	No further action required
	British and Irish Association of	• Would a positive NICE technology appraisal recommendation for tenecteplase for treating acute ischaemic stroke impact on the delivery of treatments for this condition (i.e NHS system changes)? If so, please outline how.	No further action required

Section	Consultee/ Commentator	Comments [sic]	Action
	Stroke Physicians	Yes – Tenecteplase would be used instead of alteplase – which is very likely anyway based of recent evidence and guidelines. • Would patient eligibility for tenecteplase be the same as that for alteplase (TA264)? If not, please outline how the eligibility would differ between tenecteplase and alteplase and the impact of this on NHS stroke services. Yes – alteplase sometimes must be stopped midway through the 1 hr infusion for transfer urgently for thrombectomy. Tenecteplase is a single bolus so would be greatly beneficial in this scenario particularly. It is already being used in some centres in the UK.	
	Association of British Neurologists	• Would a positive NICE technology appraisal recommendation for tenecteplase for treating acute ischaemic stroke impact on the delivery of treatments for this condition (i.e NHS system changes)? If so, please outline how. Yes. Tenecteplase would replace tPA, which is administered intravenously as a 1-minute bolus, followed by a continuous infusion over 60 minutes, which requires time to prepare and manage. Tenecteplase can be given as a single intravenous push over 5 seconds. Thus tenecteplase would make treatment easier and faster, and is likely to reduce door-to-needle time (DNT), although not all studies have confirmed this. It would also likely reduce time to mechanical thrombectomy and facilitate more rapid transfer to comprehensive thrombectomy centres. Shorter DTN times for acute ischemic stroke are associated with a reduction in morbidity, mortality, and all-cause readmission in stroke survivors.	No further action required

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		• Would patient eligibility for tenecteplase be the same as that for alteplase (TA264)? If not, please outline how the eligibility would differ between tenecteplase and alteplase and the impact of this on NHS stroke services. Yes. Eligibility for Tenecteplase would be similar to that for alteplase.	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Different strokes
Heart UK