South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Neurology

MEDICINE REVIEW:

1. Executive Summary

Date: 25 January 2018
Medicine (INN): Alteplase
Medicine (ATC): B01AD02
Indication (ICD10 code): Treatment of a patient presenting with hyper acute ischaemic stroke requiring rtPA in an extended time window of 3 hours to 4.5 hours (I63.0-6/I63.8-9/I64)
Patient population: Men and women presenting with an acute ischaemic stroke requiring rtPA in an extended time window of 3 hours to 4.5 hours
Level of Care: Adult Hospital level (secondary and regional level)
Prescriber Level: Doctors
Current standard of Care: Aspirin, oral (secondary and regional level); tPA (tertiary & quaternary level of care)
Efficacy estimates: (preferably NNT):
Effect of alteplase on a good stroke outcome (mRS 0–1) compared to control based on treatment:

- *Treatment delay*[x]
  - ≤1.5 h (90 min) ; NNT 5 ; OR 2.55 (1.44 to 4.52), p=0.0013
  - 1.5 to ≤3.0 h (91 to 180 min); NNT 9; OR 1.64 (1.12 to 2.40), p= 0.0116
  - >3.0 to ≤4.5 h (180 to 270 min); NNT 15; OR 1.34 (1.06 to 1.68), p=0.0135
- *Efficacy*[iv]
  - ≤3.0 h; OR 1.75, 95% CI 1.35–2.27; p<0.0001
  - >3.0 h to ≤4.5 h; OR 1.26, 95% CI 1.05–1.51; p=0.0132)
- *Safety*[iv]
  - Fatal ICH < 7 days: OR 7.14, 95% CI 3.98, 9.79; p<0.0001) which were in keeping with bleeding rates seen in other trials using SITS-MOST[iv] criteria (OR 6.67, 95% CI 4.11, 9.84; p<0.0001)
  - Absolute excess rate of bleeding was influenced by stroke severity; see figure 3
- *Mortality*
  - ≤3.0 h; HR 1.00 (0.81 to 1.24)
  - >3.0 h to ≤4.5 h; HR 1.14 (0.95 to 1.36)
  - >4.5h; HR 1.22 (0.99 to 1.50)
  - The early excess in mortality did not increase the overall mortality at 90 days, HR 1.11 (0.99 to 1.25; p=0.07)

Motivator/reviewer name(s): Dr A Rossouw, Prof PJ Commerford, Dr G Reubenson

PTC affiliation: East London Hospital Complex PTC

2. Name of author(s)/motivator(s)

Primary reviewer: Dr Anastasia Rossouw
Secondary reviewers: Prof PJ Commerford, Dr G Reubenson

3. Author affiliation and conflict of interest details

Primary reviewer: Affiliation: East London Hospital Complex Pharmacy Therapeutics Committee, Adult Hospital Level Committee member; *Conflict of interest:* Angels Initiative (funded by Boehringer and Ingelheim): Member of National Steering Committee, honorarium for conference and workshop attendance; Sanofi-Aventis: Honorarium for conference attendance and workshops, and training.

Note: Dr A Rossouw has a clearly significant conflict of interest, and was recused from decision-making.

Secondary reviewers:

Prof PJ Commerford: *Affiliation:* University of Cape Town, Adult Hospital Level Committee member; *Conflict of interest:* McMaster University (PHRI); Bayer: Run COMPASS (with wife) in South Africa and - remunerated by PHRI and travel support to attend study related meetings (COMPASS tests rivaroxaban).

Dr G Reubenson: *Affiliation:* National Essential Medicines List Committee member; *Conflict of interest:* Speaker fees and conference support for Sanofi and Pfizer.

4. Introduction/ Background

Recombinant tissue plasminogen activator (rtPa) had previously been approved and recommended by NEMLC for the treatment of a patient presenting with an acute ischaemic stroke provided 1) the patients presented within 3 hours of onset, and 2) where specialized neuro-radiological services i.e. Computer Tomography (CT) of the brain was available.

This was based on the National Institute of Neurological Disorders and Stroke (NINDS)[i] study group, who reported that patients with acute ischemic stroke who received alteplase (0.9 mg per kilogram of body weight) within 3 hours after the onset of symptoms were at least 30% more likely to have minimal or no disability at 3 months than those who received placebo (OR 1.9, 95 % CI 1.2-2.9).

Subsequently a pooled analysis [ix] combining data elements from six randomised control trials reported favourable functional outcome at three months when given beyond the 3-hour window.

This analysis hinted towards a possible benefit when rtPA was given beyond 3hours. This led to the conduction of the ECASS III[ii] trial, SITS-ISTR observational study[iii] and the meta-analyses by Emberson et al in 2017.

5. Purpose/Objective

To assess the efficacy and safety of alteplase (rtPA) administered to patients presenting with an acute ischemic stroke in an extended time window of 3 to 4.5 hours after the onset of stroke symptoms.

Population: patients presenting with an acute ischaemic stroke
Intervention: IV rtPA given 3 to 4.5 hours after symptom onset
Comparison: IV rtPA given in less than 3 hours
Outcomes: mortality and disability at day 90 (3-month visit)

6. Methods:

a) Data sources and search strategy

Pubmed and Cochrane

((acute[All Fields] AND ("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("infarction"[MeSH Terms] OR "infarction"[All Fields] OR "infarct"[All Fields])) AND (thrombolysis[All Fields] AND ("tissue plasminogen activator"[MeSH Terms] OR ("tissue"[All Fields] AND "plasminogen"[All Fields] AND "activator"[All Fields]) OR "tissue plasminogen activator"[All Fields]))) AND (functional[All Fields] AND outcome[All Fields])

84 records were retrieved. The titles as well as the reference lists were screened and the following records were included for this review.

- **Meta-analysis:**

  Emberson et al[iv] conducted a meta-analysis of individual patient data from 6756 patients from nine randomised trials (including NINDS A &B, ECASS I-III, ATLANTIS A & B, EPITHET and IST-3) with the primary objective to ascertain “good stroke outcome”, defined as a mRS of 0 to 1; secondary

outcomes included the rate of symptomatic and fatal intracerebral haemorrhage (sICH) within 7 days, and 90-day mortality.

- **Systematic review:**
  Wardlaw et al[v] conducted a systematic review in 2003 with subsequent updates in 2009 and 2014. The SR included 27 trials with more than 10 000 patients with an objective to determine the effectiveness and safety of thrombolytic therapy.
- **Guidelines:** European Stroke Organisation[vi], American Heart Association/ American Stroke Association[vii] and the South African guideline for the management of IS and TIA[viii].
- **Observational studies:** a) *Ahmed et al*[vii] compared outcomes in patients treated between 3 h and 4·5 h versus those treated within 3 h, who were recorded in the Safe Implementation of Treatments in Stroke (SITS), a prospective internet-based audit of the International Stroke Thrombolysis Registry (ISTR).

** OTT= the onset-to-treatment time* **NIHSS= National International Health Stroke Severity Scale*

b) Evidence synthesis

Table 1 Summary of included studies/systematic reviews and meta-analysis

Author, date	Type of study	n	Population	Comparators	Outcomes: primary and secondary	Effect sizes	Comments
Emberson et al, **meta-analysis**, 2014	Meta-analysis including 9 RCTs	6765 (3721 patients were randomly assigned to alteplase vs placebo and 3035, alteplase vs open control. Individual patient data were not available for five trials	Patients presenting with ischemic strokes up to 6h after symptom onset	Patients not qualifying for thrombolysis	Primary outcome: functional outcome at 90 days as defined by a 'good stroke outcome' (mRS of 0 to 1). Secondary outcomes included any fatal intracerebral haemorrhage within 7 days, and any symptomatic intracerebral haemorrhage (sICH) and mortality outcome at 90 days.	2110 (31%) of 6756 patients achieved a good stroke outcome (mRS of 0 or 1) at 3–6 months Within the specific subgroups relating to treatment delay, alteplase significantly increased the odds of a good outcome when given within 3·0 h (OR 1·75, 95% CI 1·35–2·27; p<0·0001) as well as 3·0 h up to 4·5h (OR 1·26, 95% CI 1·05–1·51, p=0·0132) but not after 4.5h (OR 1·15, 95% CI 0·95–1·40; p=0·15, figure 1) Although treatment with alteplase increased the likelihood of symptomatic and fatal ICH within the first 7 days HR 1.39 (95% Cl 1.16-1.67) it did not contribute to the overall mortality at 90 days (608 [17·9%] vs 556 [16·5%], HR 1·11 (95% CI 0·99–1·25); p=0·07)	The 'a priori' design was clearly stated with data extraction being conducted by the study collaborators; the statistical plan was also clearly stated and published. Individual patient data was made available from all phase 3, randomized, double-blind, placebo controlled trials were included; collaborators and pharmaceutical company were also contacted. No risk of bias table nor publication bias were assessed. Statistical analysis was appropriate. The role of funding was also declared
Wardlaw et al, systematic review, 2014	Systematic review including 27 trials	10, 187 patients	Patients presenting with ischemic strokes up to 6h after symptom onset	Patients not qualifying for thrombolysis	Overall to review the effectiveness and safety of thrombolysis given for acute ischaemic stroke	Thrombolysis mostly given <6h of symptom onset significantly reduces the proportion of patients dead or dependent at 6mo, odds ratio (OR) 0.85, 95% confidence interval (CI) 0.78 to 0.93). Treatment within three hours of stroke was more effective in reducing death or dependency (OR 0.84, 95% CI 0.77 to 0.93) without any increase in death (OR 0.99,	Heterogeneity existed between the trials.

						95% CI 0.82 to 1.21; 11 trials,2187 participants, figure 2) There was a three -fold increase in symptomatic intracranial haemorrhage in those who received tPA vs control (7.5% vs 1.7%) (OR 3.75, 95%CI 3.11 to 4.51, P < 0.00001)	
Lees et al, systematic review, 2010	Updated pooled analysis, previous 6 trials with ECASS III and EPITHET	3670 patients, 2775 from previous pooled analysis with 821 from ECAS III and 100 from EPITHET trial	Inclusion of patients based on ischaemic confirmed after CT scan had excluded the presence of an intracerebral bleed AND confirmed stroke onset to start of treatment (OTT)	Excluded those with ICH AND exclusion criteria for tPA, see Appendix A	Good favourable outcome at 90 days (mRS 0-1 alone) AND composite measure consisting of three neurological function scores of modified Rankin Scale (0–1), Barthel Index (95–100), and NIHSS (0–1).	Odds of a favourable 3-month outcome was 2·55 (95% CI 1·44–4·52) for 0–90 min, 1·64 (1·12–2·40) for 91–180 min, 1·34 (1·06–1·68) for 181–270 min, and 1·22 (0·92–1·61) for 271–360 min in favour of the alteplase group. Magnitude of effect diminishes with increases in time (NNT=4.5 at 90mnis, NNT=9 at 180mins and NNT=14 at 270mins). Parenchymal hemorrhages were noted in 5.2% vs 1.0%, OR 5·37 (95% CI 3·22–8·95); p= <0·0001 of patients over the whole time continuum (0-360mins). The incidence of all intracerebral hemorrhages (both fatal and non-fatal) were seen in 24.2 vs 32.5% of cases, OR 1.60, (95% CI 1·37–1·87); p=<0·0001	Included trials were all similar in their primary outcomes but differed in the way they were measured, hence the measurement of the composite endpoint. Data extraction plan, statistical analysis clearly defined. No risk of biases table included. EPITHET RCT included outcome rsults from patients from 180-360 min only. Analyses was done including and excluding EPITHET data and findings were similar.
ATLANTIS, ECASS NINDS rt-PA Study Group Investigators, 2004	Pooled analysis, including 6 trials (NINDS I & II ECASS I & II and ATLANTIS A&B)	2775 participants across 18 hospitals	Patients presenting with ischemic strokes >300 minutes after symptom onset, clearly defined time of symptom onset and a CT scan	Patients with no clearly defined ischaemic stroke in CT	Functional outcome and 90 days as defined by a mRS of 0 to 1 Rate of symptomatic ICH as defined elsewhere Mortality rate	OTT: Even though the odds of a favourable (mRS 0-1) 3-month outcome increased as OTT decreased (p=0·005), a benefit was still evident in favour of the rtPA group beyond the 3 hour mark: OR 2.8 (95% CI 1.8–4.5) for 0–90	Included trials were all similar in their outcomes measures but differed in the definition of primary outcome and the definition of an intracranial bleed

			of the head that excluded a hemorrhage		*patients with moderate stroke severity (NIHSS=11) and OTT median=243min	min, 1.6 (1.1–2.2) for 91–180 min, 1.4 (1.1–1.9) for 181–270 min, and 1.2 (0.9–1.5) for 271–360 min. NIHSS: A greater proportion of patients with moderate to severe strokes were treated in the extended time period, 3.0h-4.5h (161 vs 302 vs 309) mRs: The proportion of patients with good functional outcome at the 3 time points showed little variation (41 vs 43 vs 37). The proportion of patient with a poor outcome also showed little variation between the three time groups with no difference in mortality. HR when adjusted for NIHSS was 1·0 for the 0–90, 91–180, and 181–270 min intervals; for 271–360 min it was 1·45 (1·02–2·07). Haemorrhage was seen in 82 (5·9%) rt-PA patients and 15 (1·1%) controls (p<0·0001); this rate however did not differ from previously published bleeding rates.	

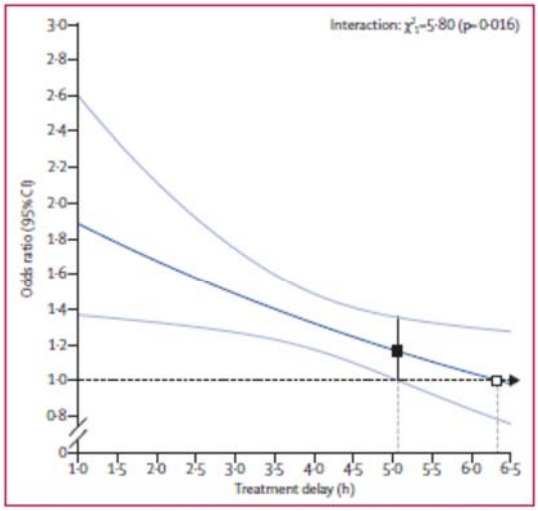

Figure 1: **Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1)**
The solid line is the best linear fit between the log odds ratio for a good stroke

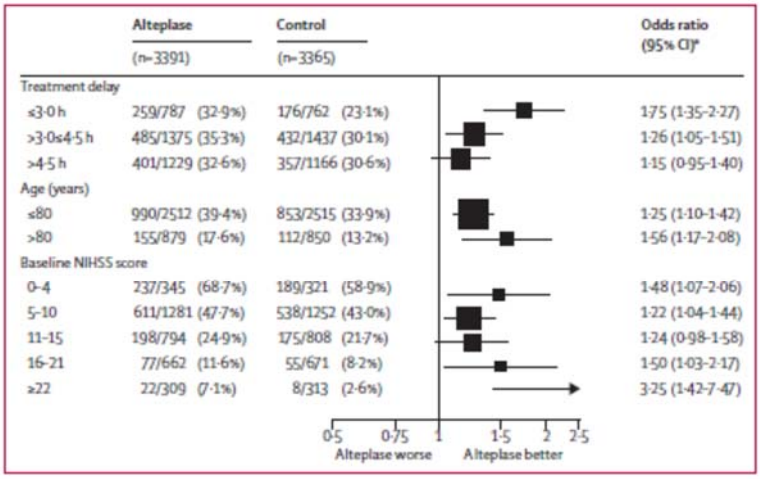

Figure 2: **Effect of alteplase on good stroke outcome (mRS 0–1), by treatment delay, age, and stroke severity**
*For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not for possible interactions with those characteristics). mRS=modified Rankin Scale.

Figure 1. Effect of alteplase on good stroke outcome (mRS 0-1) by timing (A), treatment delay (B), age (B) and stroke severity (B), Emberson et al, MA, 2014

Analysis 1.6. Comparison 1 Any thrombolytic agent versus control, Outcome 6 Death or dependency at the end of follow-up.

Review: Thrombolysis for acute ischaemic stroke

Comparison: 1 Any thrombolytic agent versus control

Outcome: 6 Death or dependency at the end of follow-up

Study or subgroup	Thrombolysis n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
3 Intravenous rtA versus control					
Mori 1992	11/19	10/12		0.3 %	0.32 [0.07, 1.48]
NINDS 1995	155/312	192/312		7.2 %	0.62 [0.45, 0.85]
ECASS 1995	171/313	185/307		7.1 %	0.79 [0.58, 1.09]
ECASS II 1998	187/409	211/391		9.4 %	0.72 [0.55, 0.95]
ATLANTIS B 1999	141/307	135/306		7.1 %	1.08 [0.78, 1.48]
ATLANTIS A 2000	64/71	56/71		0.9 %	2.35 [0.95, 5.82]
Wang 2003	29/67	26/33		1.0 %	0.24 [0.10, 0.56]
ECASS 3 2008	140/418	155/403		8.8 %	0.81 [0.61, 1.07]
EPITHET 2008	28/51	29/49		1.2 %	0.84 [0.38, 1.85]
IST3 2012	961/1515	986/1520		32.6 %	0.94 [0.81, 1.09]
Subtotal (95% CI)	**3482**	**3404**		**75.6 %**	**0.84 [0.77, 0.93]**
Total events: 1887 (Thombolysis), 1985 (Control)					

Heterogeneity: Chi² = 24.54, df = 9 (P = 0.004); I² =63%

Test for overall effect: Z = 3.42 (P = 0.00062)

Figure 2. Effect of thrombolysis on death and dependency at 90 days, Wardlaw et al, SR, 2014

7. Discussion

Overall results:

Meta analyses*:* The primary objective was to ascertain "good stroke outcome", as defined as a mRS of 0 to 1; secondary outcomes included symptomatic intracerebral haemorrhage (sICH), fatal intracranial haemorrhage within 7 days, and 90-day mortality. 2110 (31%) of 6756 patients achieved a good stroke outcome (mRS of 0 or 1) at 3–6 months with the odds of a good outcome noted with earlier treatment. Outcome, within subgroups of treatment delay, alteplase significantly increased the odds of a good outcome when given within 3·0 h (OR 1·75, 95% CI 1·35–2·27; p<0·0001) or after 3·0 h up to 4·5 h (OR 1·26, 95% CI 1·05–1·51, p=0·0132), but not after 4·5 h (OR 1·15, 95% CI 0·95–1·40; p=0·15; figure 1). Age did not change the effect of alteplase on the odds of a good outcome. Although treatment with alteplase increased the likelihood of symptomatic ICH it did not contribute to the overall mortality at 90 days (608 [17·9%] vs 556 [16·5%], HR 1·11 (95% CI 0·99–1·25); p=0·07; figure 3).

Systematic reviews: Thrombolytic therapy, mostly administered up to six hours after ischaemic stroke, significantly reduced the proportion of participants who were dead or dependent (modified Rankin 3 to 6) at three to six months after stroke (odds ratio (OR) 0.85, 95% confidence interval (CI) 0.78 to 0.93).

Pooled analysis: Although the treatment effect diminished as the OTT increased, a benefit was still evident for patients treated between 3·0 h to 4·5 h OR 1.4, 95% Cl 1.1–1.9 for 181–270 min with stroke severity having little to no effect on treatment outcome.

Observational study: SITS-ISR observational study[vii] conducted between 2002 and 2007 where 664 patients who presented with ischaemic stroke were given intravenous alteplase (0·9 mg/kg total dose) between 3 h and 4·5 h with 11 865 patients treated within 3 h. Outcome measures were symptomatic intracerebral hemorrhage within 24 h, mortality and independence (modified Rankin scale of 0–2) at 3 months. No significant differences were recorded between the 3–4·5-h cohort and the within 3-h cohort for any outcome measure:

- rate of symptomatic intracerebral haemorrhage: 2·2% (14 of 649) versus 1·6% (183 of 11 681) (odds ratio [OR] 1·18 [95% CI 0·89–1·55], p=0·24; adjusted OR 1·32 [1·00–1·75], p=0·052);
- mortality: 12·7% (70 of 551) versus 12·2% (1263 of 10 368) (OR 1·02 [0·90–1·17]; p=0·72; adjusted OR 1·15 [1·00–1·33]; p=0·053);
- independence: 58·0% (314 of 541) versus 56·3% (5756 of 10231) (OR 1·04 [0·95–1·13], p=0·42; adjusted OR 0·93 [0·84–1·03], p=0·18).

Quality of the studies:

All the studies were of good quality with clearly defined outcome measures, data extraction and statistical plans. The SR (Wardlaw et al) was the only study that included a risk of biases table.

Safety concerns:

Subgroup analyses as reported by Emberson et al indicated that those patients receiving alteplase who presented with more severe strokes (high NIHSSs) were more likely (OR 7·14, 95% CI 3·98–12·79; p<0·0001) to have a fatal ICH within 7 days of receiving alteplase; this did not have an effect on the overall mortality at 90 days.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [x] Not confident [ ] Uncertain [ ]</td><td>Evidence generation supported by a meta-analysis, SR and RCTs</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td>There was a three-to-four fold increase in fatal ICH within 7 days but with no impact on overall mortality at 90 days</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the outcomes?

Minor [X] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [x]</td><td>Limited data available about the patient numbers currently being treated with rtPA in South Africa as well as the proportion of patients with residual disability

Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)*</th></tr><tr><td>Alteplase 0.9 mg/kg (modelled on 70 kg adult) = 63 mg.</td><td>R 16 018.05 to 9 610.03</td></tr></table>*60% to 100 % of SEP - SEP database 22 October 2018 ; alteplase 50 mg, R8 009.03 to R4 8015.42
Additional resources:
Literature review of cost-effectiveness analyses of rtPA for acute ischaemic stroke showed that:
• IV rtPA within 0–3 hours after the onset of stroke was cost-saving while improving QALYs during lifetime.
• Use of IV rtPA within 3 to 4.5 hours after the onset of stroke increased costs, but improved QALYs over the lifetime; and was shown to be cost-effective over 30 years or a lifetime (US$6255/QALY to US$21 978/QALY).
Studies were heterogeneous and limitations included insufficient data for accurate cost-effectiveness estimates; lack of generalisability because of data limitations; use of multiple data sources because of limited data; lack of long-term mortality and cost data as well as insufficient up-to-date outcome and cost data.
Study population includes New Zealand, USA, Denmark, China, Spain, Australia, UK, Canada.
Reference: Joo H, Wang G, George MG A literature review of cost-effectiveness of intravenous recombinant tissue plasminogen activator for treating acute ischaemic stroke Stroke and Vascular Neurology 2017;2:doi: 10.1136/svn-2016-000063</td></tr>
<tr><td>EQUITY</td><td>What would be the impact on health inequity?

Yes [X] No [ ] Uncertain [ ]</td><td>Access to rtPA will be limited to “stroke ready hospitals”, i.e. regional and or tertiary level care facilities where neuro-imaging (CT brain) facilities, trained staff and an integrated care pathway exists.</td></tr>
</table>

FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☐	**Note:** That this option would only be feasible in stroke-ready facilities where appropriate neuro-imaging facilities acute stroke care protocols, and teams trained on acute stroke care guidelines, are available.

	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
Type of recommendation	☐	☐	☐	☐	☐

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends that rtPA time window not be extended from 3 to 4.5 hours for the treatment of acute ischaemic stroke. rtPA is only to be considered for use at facilities where specialised neuro-radiological services and relevant expertise that are available within the prescribed three hours.

Rationale: Cost-benefit beyond 3 hours decreases and rtPA is expensive. rtPA can only be administered where specialised neuro-radiological services are available. Alteplase is currently included on the Tertiary & Quaternary EML and Provincial PTCs have the mandate to authorise use at appropriate levels by relevant specialists.

Level of Evidence: I Meta analysis, Systematic review, Guidelines, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm/safety	Price reduction
☐	☐	x

VEN status: (T&Q EML)

Vital	Essential	Necessary
☐	x	☐

NEMLC MEETING OF 6 DECEMBER 2018:

The NEMLC accepted the Adult Hospital Level Committee's recommendation, above and further recommended that a registry be set up to determine actual use of tPA throughout the country. This would also assist in identifying facilities that provide thrombolytic therapy for management of stroke (and training needs as required).

M & E considerations: Patients numbers in SA treated within and beyond 3 hour marked regarding outcomes (mortality and morbidity); numbers of sICH in SA

Research priorities : Establishment of a national stroke registry; establishments of integrated care pathways in SA, health economic impact with numbers needed to treat to reduce disability. Research regarding functional emergency stroke units are needed. Determine the actual number patients receiving thrombolysis in SA, the number of patients currently living with disability and report on the outcomes.

APPENDIX A: EXCLUSION CRITERIA FOR THROMBOLYSIS

History of stroke or serious head trauma within the preceding 3 months; major surgery within 14 days; gastrointestinal or genitourinary bleeding within 21 days; arterial puncture at a non-compressible site within 7 days; any history of intracranial haemorrhage; present symptoms suggestive of subarachnoid haemorrhage; or systolic blood pressure consistently more than 185 mm Hg or diastolic blood pressure more than 110 mm Hg (or patients needing aggressive treatment to lower their blood pressure to these levels); patients who were taking oral anticoagulants or heparin within 48 h and who had a raised partial thromboplastin time and a prothrombin time more than 15 s or platelet count below 100g/dL.

References:

[i] The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581-7. https://www.ncbi.nlm.nih.gov/pubmed/7477192

[iv]Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008 Sep 25;359(13):1317-29. https://www.ncbi.nlm.nih.gov/pubmed/18815396

[iii] Wahlgren N, Ahmed N, Dávalos A, Hacke W, Millán M, Muir K, Roine RO, Toni D, Lees KR; SITS investigators. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet. 2008 Oct 11;372(9646):1303-9. https://www.ncbi.nlm.nih.gov/pubmed/18790527

[iv] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al.; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014 Nov 29;384(9958):1929-35https://www.ncbi.nlm.nih.gov/pubmed/25106063

[v] Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Jul 29;(7):CD000213. https://www.ncbi.nlm.nih.gov/pubmed/25072528

[vi] European Stroke Organisation. Update Guidelines January 2009. http://www.eso-stroke.org/pdf/ESO_Extended_Thrombolysis_KSU. pdf (accessed April 5, 2010).

[vii] Del Zoppo GJ, Saver J, Jauch EC, Adams HP, on behalf of the American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke 2009; 40: 2945–48. https://www.ncbi.nlm.nih.gov/pubmed/19478221

[viii] Bryer A, Connor M, Haug P, Cheyip B, Staub H, Tipping B, Duim W, Pinkney-Atkinson V. South African guideline for management of ischaemic stroke and transient ischaemic attack 2010: a guideline from the South African Stroke Society (SASS) and the SASS Writing Committee. S Afr Med J. 2010 Nov 10;100(11 Pt 2):747-78. https://www.ncbi.nlm.nih.gov/pubmed/21081029

[ix] The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators,. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004; 363: 768–74. https://www.ncbi.nlm.nih.gov/pubmed/15016487

[X] Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, for the ECASS, ATLANTIS, NINDS, and EPITHET rt-PA Study Group Investigators*. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375: 1695–703. https://www.ncbi.nlm.nih.gov/pubmed/20472172

[xi] Joo H, Wang G, George MG A literature review of cost-effectiveness of intravenous recombinant tissue plasminogen activator for treating acute ischaemic stroke Stroke and Vascular Neurology 2017;2:doi: 10.1136/svn-2016-000063