Ballarat Health Services

DRUG GUIDELINE

Alteplase (Intravenous – pulmonary embolism)

HIGH RISK MEDICATION

SCOPE (Area): **FOR USE IN:** ED, Intensive Care Unit
EXCLUSIONS: Paediatrics (seek Paediatrician advice) and other wards
SCOPE (Staff): Medical, Nursing and Pharmacy

This Drug Guideline must be used in conjunction with CPG0087 Investigation And Initial Management Of Patients With Suspected Pulmonary Embolism in the Emergency Department.

These guidelines do not refer to other indications for alteplase, refer as appropriate to Alteplase (Intravenous – ischaemic stroke) (DRG0013), Alteplase in STEMI (DRG0065) or Alteplase - Restoring Patency to Central Venous Access Devices (CVADs) (DRG0055).

Alteplase is also known as recombinant tissue plasminogen activator, rt-PA or t-PA.

BRAND NAMES
Actilyse®.

PHARMACOLOGY AND PHARMACOKINETICS
Alteplase binds to the fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis (clot breakdown). Alteplase will cause fibrinolysis in any clot in the body, which may induce brain haemorrhage or other bleeding. Alteplase is cleared rapidly by the liver (after the infusion has been terminated, more than 50% will be cleared in the following 5 minutes), however the effect of alteplase will gradually diminish but continue for at least 24 hours.

INDICATIONS
All indications require Consultant advice.

- **Pulmonary embolism <u>with</u> haemodynamic compromise (massive pulmonary embolism) defined by:**
  - **Imminent or actual cardiac arrest due to pulmonary embolism requiring CPR**
  - **Obstructive shock** – systolic blood pressure (SBP) less than 90 mmHg or vasopressors required to maintain SBP greater than 90 mmHg despite adequate filling status **AND** end-organ hypoperfusion
  - **Persistent hypotension** – SBP less than 90 mmHg OR reduction in SBP greater than 40 mmHg for longer than 15 minutes, not due to new onset arrhythmia, hypovolaemia, or sepsis
  - **Persistent profound bradycardia (heart rate less than 40 bpm) or tachycardia (heart rate greater than 140 bpm) with signs or symptoms of shock (pallor, sweating, altered mentation, delayed central capillary return)**
- **Pulmonary embolism <u>without</u> haemodynamic compromise (submassive pulmonary embolism)** – may be considered in patients with evidence of right ventricular strain, as demonstrated by echocardiography or elevated troponin and/or severe hypoxaemia.

CONTRAINDICATIONS

In the situation of imminent/actual cardiac arrest from a massive pulmonary embolus requiring CPR, there are no absolute contraindications to thrombolysis.

Absolute contraindications:

- Active bleeding or bleeding diathesis (excluding menses), coagulopathy including inherited (e.g. haemophilia) and acquired causes (decompensated liver disease, disseminated intravascular coagulation (DIC), platelets less than 80 x 10^9/L).
- Significant closed head or facial trauma within 3 months.
- Suspected aortic dissection (including new neurological symptoms).
- Ischaemic stroke within 3 months.
- Intracranial haemorrhage in the last 12 months.
- Known structural cerebral vascular lesion (e.g. arteriovenous malformation, aneurysm).
- Known malignant intracranial neoplasm (primary or metastatic).
- Cranial or spinal surgery within 3 weeks.

Relative contraindications:

- Current use of anticoagulants. With warfarin the higher the international normalised ratio (INR) above 1.7, the higher the risk of bleeding.
- Recent non-compressible vascular punctures, obstetric delivery or organ biopsy (within 10 days).
- Recent major (e.g. intrathoracic, intra-abdominal) surgery (within 3 weeks).
- Traumatic or prolonged (greater than 10 minutes) cardiopulmonary resuscitation (within 10 days).
- Recent (within 4 weeks) internal bleeding (e.g. gastrointestinal or urinary tract haemorrhage).
- Active peptic ulcer.
- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (greater than 180 mmHg systolic or greater than 110 mmHg diastolic)
- Ischaemic stroke greater than 3 months ago, dementia, or known intracranial abnormality not covered in absolute contraindications
- Pregnancy or postpartum less than 2 weeks – seek Specialist advice.
- Serious hypersensitivity reaction to alteplase or gentamicin (trace amount present in vial).

PRECAUTIONS

In the following conditions, the risk of bleeding with alteplase may be increased and should be weighed against the anticipated benefits:

- Recent trauma.
- High likelihood of left heart thrombus, e.g. mitral stenosis with atrial fibrillation.
- Acute pericarditis.
- Subacute bacterial endocarditis.
- Acute pancreatitis.
- Haemostatic defects, including those secondary to severe hepatic or renal disease.
- Severe hepatic dysfunction.
- Septic thrombophlebitis or occluded AV cannula at infected site.
- Arterial aneurysms, arterial/venous malformations.
- Neoplasm with increased bleeding risk.
- Advanced age, which may increase the risk of intracerebral haemorrhage.
- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions.
- Recent administration of GP IIb/IIIa inhibitors (eptifibatide, tirofiban).

Other:

- **Bleeding** – most common adverse reaction with alteplase (risk is further increased by heparin), see Adverse Effects.
- **Intrathecal or epidural analgesia or anaesthesia, or lumbar puncture** – risk of epidural haematoma which can cause paralysis, seek specialist advice before proceeding for patients who have recently had neuraxial procedures performed, or require neuraxial procedures after thrombolysis. See CPP0729 Perioperative Management of Anticoagulant & Antiplatelet Agents.
- **Renal failure** – arginine present in the vials may lead to hyperkalaemia.
- **See Nursing Practice Points for a range of Precautions** that apply during alteplase administration and for the next 12 to 24 hours.

PREGNANCY AND BREASTFEEDING

Seek specialist advice before prescribing, information may update regularly. Refer to the Royal Women's Pregnancy and Breastfeeding Medicines Guide for more information.

DRUG INTERACTIONS

- **The following medications given in combination with alteplase increase the risk of bleeding. Monitor closely for signs of bleeding. This risk may continue for several days after discontinuation of agent. See Dosage and Administration for further information:**

Other thrombolytics	tenecteplase, urokinase
Heparin and low molecular weight heparins	dalteparin, danaparoid, enoxaparin, heparin, nadroparin
Direct thrombin inhibitors	argatroban, bivalirudin, dabigatran
Vitamin K antagonists	warfarin
Factor Xa inhibitors	apixaban, fondaparinux, rivaroxaban
Glycoprotein IIb/IIIa inhibitors	eptifibatide, tirofiban
Non-steroidal anti-inflammatory agents	Aspirin (low dose OK), diclofenac, ibuprofen, indometacin, ketoprofen, ketorolac, mefenamic acid, naproxen, piroxicam Note: Selective NSAIDs (celecoxib, etoricoxib, meloxicam, parecoxib) do not directly affect clotting, but increase the risk of gastrointestinal bleeding
Selective serotonin reuptake inhibitors	citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Serotonin and Noradrenaline Reuptake Inhibitors	desvenlafaxine, duloxetine, venlafaxine
Prostacyclin analogues	epoprostenol, iloprost
Other	anagrelide, clopidogrel, dipyridamole, prasugrel, protein C concentrate (human), ticagrelor
Herbal medications	bilberry, bromelain, embilica, garlic, ginger, ginkgo biloba, ginseng (american), ginseng (panax), ginseng (siberian), policosanol

- **Tranexamic acid** – decreased effectiveness of each agent.
- **ACE inhibitors and Angiotensin II antagonists –** increased risk of experiencing an anaphylactoid reaction with alteplase. Monitor.
- **Glyceryl trinitrate –** may increase hepatic blood flow, leading to increased clearance of alteplase. This may reduce the thrombolytic efficacy of alteplase – monitor for adequate reperfusion and possible reocclusion. Use the lowest dose of glyceryl trinitrate possible.

DOSAGE AND ADMINISTRATION

Patients require ICU admission (and ECG monitoring or telemetry) for 24 hours after administration of alteplase. For administration

- **only in Intensive Care Unit or ED**

Only to be prescribed by Intensive Care, Emergency Department or Medical Registrar after discussion with a Consultant. Contraindications and Precautions above MUST be reviewed prior to prescribing, and consent obtained from patient/family where possible.

Systemic thrombolysis in the setting of pulmonary embolism is associated with a risk of major bleeding (approximately 6%) and intracranial haemorrhage (2 to 3%).

PRIOR to administering thrombolysis, ensure that blood is taken for FBE, INR, APTT, Fibrinogen, LFTs, U&Es, troponin and Group and Hold.

Alteplase is the only thrombolytic approved for use at GH-B for pulmonary embolism.

Start all candidates for thrombolysis of pulmonary embolism on a heparin infusion during assessment (as per Heparin Drug Guideline DRG0038). Suspend heparin during alteplase administration. Restart heparin (without a bolus) after alteplase is completed, and the APTT is less than twice the upper limit of normal. See ALTEPLASE in Pulmonary Embolism Flowchart (page 6).

Administer alteplase via CVC, midline or peripheral line. Requires a dedicated line, do not mix with any other drugs or fluids. Only compatible with sodium chloride 0.9%, incompatible with heparin, as such two sites of IV access are required.

Low dose aspirin may be used if indicated. Do not administer other antiplatelets, low molecular weight heparins (e.g. enoxaparin), warfarin, direct oral anticoagulants (DOACs – apixaban, rivaroxaban, dabigatran) in the acute phase, during alteplase administration and for 24 hours after alteplase administration.

If any signs of bleeding (intracranial or extracranial) during alteplase administration

- **cease alteplase and heparin administration**
- **contact relevant Registrar immediately**

On ED imprest alteplase must be stored separate to other thrombolytics with a sign stating 'For thrombolysis of Pulmonary Embolism ONLY'.

Document orders on the following medication charts:

- **Alteplase initial doses: National Standard Medication Chart MR/700.2, Once Only orders section**
- **IV infusion: Adult Intravenous Orders MR/645.0**
- **Heparin orders: Heparin IV Infusion Chart MR/700.3**

Dosing (see also ALTEPLASE in Pulmonary Embolism Flowchart on next page):

<table>
<tr><th></th><th colspan="2">Non-arrest</th><th colspan="2">Imminent or actual cardiac arrest (requiring CPR)</th></tr>
<tr><th>Weight</th><th>Less than 65 kg</th><th>65 kg or more</th><th>Less than 83 kg</th><th>83 kg or more</th></tr>
<tr><td>Total dose</td><td>1.5 mg/kg</td><td>100 mg</td><td colspan="2">1 to 2 doses depending on response</td></tr>
<tr><td>Initial dose</td><td colspan="2">Loading dose of 10 mg IV injection over 1 minute</td><td>0.6 mg/kg IV injection undiluted over 2 minutes</td><td>50 mg IV injection over 2 minutes</td></tr>
<tr><td rowspan="2">Subsequent dose</td><td>Remainder of total dose as IV infusion over 2 hours (=1.5 mg/kg MINUS 10 mg)</td><td>90 mg IV infusion over 2 hours</td><td colspan="2" rowspan="2">Consider repeating initial dose ONCE only if no return of spontaneous circulation after 15 minutes</td></tr>
<tr><td colspan="2">Dilute infusion dose in sodium chloride 0.9% bag, final volume of 100 mL</td></tr>
<tr><td colspan="5">Maximum dose is weight based and not to exceed 2 doses (initial and subsequent) or 100 mg total</td></tr>
</table>

Vial selection:

High cost medication. Prepare only once alteplase confirmed to proceed.

- **Imminent or actual arrest:** use the 50 mg vial. Prepare the initial dose only as the subsequent dose may not be required.
- **Non-arrest:** select vials as per the table below. Prepare BOTH initial (load) and subsequent infusion doses prior to commencing alteplase, as the infusion commences immediately after the load is completed.

Total Dose (max 100 mg)	Number of vials required to obtain calculated dose from
50 mg or less	50 mg x 1
51 to 60 mg	50 mg vial x1 and 10 mg vial x1
61 to 70 mg	50 mg vial x1 and 10 mg vial x2
71 to 80 mg	50 mg vial x1 and 10 mg vial x3
81 to 100 mg	50 mg vial x2

Vial reconstitution (see package insert for pictorial description):

Reconstitute alteplase to a **final concentration of 1 mg/mL** using the diluent provided in the box (preservative free water for injections).

The 50 mg vial has a mixing cannula in the box, reconstitute using the following steps:

- Remove the caps off both vials (alteplase powder and sterile water for injections)
- Use the mixing cannula to pierce the bung of the water for injections
- Invert the alteplase powder vial and pierce its bung using the other end of the mixing cannula whilst the water for injections vial stays flat on the bench i.e. water for injections on the bottom, and alteplase powder on top
- Invert both vials with the mixing cannula still attached so the alteplase powder is now on the bottom, and the water for injection on top
- Allow two minutes for the water for injection to transfer and powder to dissolve
- One or two gentle swirling actions may be required to assist with mixing, but DO NOT SHAKE.
- Slight foaming may occur but usually settles if the vial is left standing undisturbed for several minutes. The prepared solution is a colourless to pale yellow transparent solution.

ALL DOSES REQUIRE AN INDEPENDENT DOUBLE CHECK

ALTEPLASE in Pulmonary Embolism Flowchart

All **ALTEPLASE** doses are to be prescribed by the ED, ICU or Medical Registrar after discussion with a Consultant
Maximum total dose is 100 mg including initial dose
If patient is already on a heparin infusion, suspend heparin infusion during alteplase administration
ALL DOSES REQUIRE AN INDEPENDENT SECOND CHECK

Non-arrest

Dose

65 kg or greater: 10 mg IV **loading dose** over 1 minute, then 90 mg by IV infusion over 2 hours.

Less than 65 kg: total 1.5 mg/kg with 10 mg IV **loading dose** over 1 minute, then remainder of dose by IV infusion over 2 hours (e.g. 50 kg patient = max 75 mg given as 10 mg load over 1 minute and then 65 mg over 2 hours)

Prepare **both** loading and infusion doses
Select number of vials required as per table in DRG0052.
Reconstitute to a final concentration of 1 mg/mL

Loading dose: Draw up 10 mg (10 mL) alteplase into a 10 mL syringe. Attach label. Do not dilute further.

Infusion: Draw up the required volume of alteplase into 1 to 2 x 50 mL syringes. Withdraw and discard the same volume from a 100 mL sodium chloride 0.9% bag. Add alteplase. Attach label.

SUSPEND HEPARIN INFUSION

Give **loading dose**
10 mg (10 mL) undiluted IV injection by hand over 1 minute

Give IV infusion **immediately** after the loading dose
Use alteplase solution to prime the line
Administer infusion dose diluted to 100 mL over 2 hours (50 mL/hr) via Alaris pump module with Guardrails

Select 'Alteplase' then 'Pulmon Emboli <65 kg' OR 'Pulmon Emboli 65kg+'

Flush line with 30 mL sodium chloride 0.9% at 50 mL/hr.
Note: due to line volume and priming, the bag will run out before 2 hours has elapsed. The slow flush is required to administer the entire dose.

Imminent or actual cardiac arrest

Dose

83 kg or greater: 50 mg IV injection over 2 minutes
Less than 83 kg: 0.6 mg/kg IV injection over 2 minutes
Reconstitute 50 mg vial to a final concentration of 1 mg/mL

Actual body weight	ALTEPLASE dose (0.6 mg/kg) 1 mg/mL solution
40 kg	24 mg (24 mL)
45 kg	27 mg (27 mL)
50 kg	30 mg (30 mL)
55 kg	33 mg (33 mL)
60 kg	36 mg (36 mL)
65 kg	39 mg (39 mL)
70 kg	42 mg (42 mL)
75 kg	45 mg (45 mL)
80 kg	48 mg (48 mL)
Greater than 83 kg	50 mg (50 mL)

Give initial dose **immediately**
Give undiluted IV injection by hand over 2 minutes
Flush with 20 mL sodium chloride 0.9%

Return of spontaneous circulation after 15 minutes?

YES

NO

Consider repeating dose ONCE only
Total maximum 100 mg

Repeat APTT immediately

APTT less than twice upper limit of normal

Commence heparin infusion with **no bolus** as per Heparin IV Infusion Chart (MR/700.3) OR if heparin infusion was paused for thrombolysis, restart at the previous rate (**no bolus**).

APTT greater than twice upper limit of normal

DO NOT start or restart heparin
Repeat APTT in 4 hours

General Administration Information

- **Infusion pump:** BD Alaris PCU with pump module and Guardrails
- **Routes of administration:**

IV injection:	Yes (bolus)
IV intermittent infusion:	Yes
IV continuous infusion:	No
IM injection:	No
Subcut injection:	No

- **Compatible/incompatible IV drugs/fluids:**
  Consult the Australian Injectable Drugs Handbook ('Yellow book') in your ward area. **Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.**

MONITORING (INCLUDING BLOOD TESTS)

- PRIOR to administering thrombolysis, ensure that blood is taken for FBE, INR, APTT, Fibrinogen, LFTs, U&Es, troponin and Group and Hold.
- APTT immediately after alteplase infusion has finished.
- Repeat bloods as ordered by the Medical staff.

NURSING PRACTICE POINTS

- **Patient to remain in ED/ICU for 24 hours post alteplase infusion.**
- **Patients should receive supplemental oxygen.**
- **ECG monitoring or telemetry is mandatory for 24 hours after administration of alteplase.**
- **If a change in GCS of greater than 1 point,** cease alteplase or heparin administration, and contact the ED/ICU/Medical Registrar immediately for assessment of possible intracranial haemorrhage.
- **If any signs of internal or external bleeding (see more information below under observations)**, cease alteplase or heparin infusions and contact ED/ICU/Medical Registrar immediately. See DRG0030 Protamine if heparin reversal is required.
- **If any signs of allergy are detected** during alteplase administration, cease alteplase infusion and contact the ED/ICU/Medical Registrar immediately.
- **Perform the following observations:**
  - Monitor continuously for signs of **internal** bleeding (tachycardia, hypotension, pallor, restlessness, lower back pain, new muscle weakness/numbness in lower extremities).
  - Monitor hourly for signs of **external** bleeding (e.g. IV sites, gums, wounds, epistaxis) .
  - Urine full ward test each void or 6 hourly for indwelling catheter, monitoring for bleeding.
  - Blood pressure (with manual blood pressure cuffs to avoid bruising from over-inflation from automatic blood pressure machines), HR, RR, $Sa0_2$, temperature and neurological observations:
    - every 15 minutes during the alteplase infusion;
    - then every 30 minutes for 2 hours;
    - then hourly until 6 hours from start of alteplase;
    - then every 2 hours until 12 hours from start of alteplase;
    - then every 4 hours until 24 hours from start of alteplase.
  - Strict maintenance of fluid balance chart.
  - Strict bowel chart to monitor for bleeding.
- **Strict rest in bed** during alteplase infusion, and for 12 hours after.
- **The following precautions must be followed** during alteplase infusion, and for 24 hours after:
  - Do not administer antiplatelets (other than low dose aspirin if indicated), low molecular weight heparins (e.g. enoxaparin), DOACs or warfarin.
  - Venepuncture should be avoided, with blood tests taken from the IV cannula if possible.
  - Arterial puncture should be avoided, if necessary use an upper extremity vessel that is

accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.
  - Avoid the use of rigid catheters, intramuscular injections, other invasive procedures and non-essential handling of the patient.
  - Do not insert or remove indwelling catheters or nasogastric tubes, except on advice of Intensive Care/ED/Medical Registrar.
  - Supplemental oxygen must be administered via a mask as nasal prongs can cause nasal mucosa damage.
  - Falls prevention strategies.
  - Use only electric shavers.
- All injections and infusions are to be labelled as per CPP0222 User Applied Labelling Of Injectable Medicines, Fluids And Lines.

ADVERSE EFFECTS

- **Serious bleeding** – Intracranial haemorrhage such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, intracranial haematoma, subarachnoid haemorrhage with associated neurological symptoms (2-3%). Gastrointestinal (1-10%), genitourinary (1-10%), epistaxis or other respiratory (1-10%), retroperitoneal (less than 1%), pericardial (less than 1%), hepatic (less than 0.1%), eye (less than 0.01%). This may present as shock (falling blood pressure, tachycardia etc).
- **Bruising or superficial bleeding** - occurs in greater than 10% of patients, particularly at sites of minor trauma or venepuncture.
- **Allergic reactions** - have been reported in less than 1% of cases with alteplase, and may range from mild to anaphylactoid. Patient may develop swelling around the mouth and tongue during the infusion. There has been an association with concurrent use of ACE inhibitors with Alteplase and the incidence of allergic reactions.
- **Other** – blood pressure decreased (greater than 10%), body temperature increased (1-10%), requiring blood transfusion (1-10%), embolism (less than 1%), cholesterol embolism (less than 0.1%). Incidence unknown: pulmonary re-embolisation, pulmonary oedema, pleural effusion, hypotension.

DRUG PRESENTATIONS AND STORAGE

Alteplase 10 mg and 50 mg vials.
Store below 30°C. Protect vials from light.
