DRUG GUIDELINE

Alteplase (Intravenous – pulmonary embolism)

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 Guidelines must be used in conjunction with CPG0087 Pulmonary Embolism – Diagnosis & Initial Management of Patients with Suspected Pulmonary Embolism.

These guidelines do not refer to other uses of alteplase, instead refer to Alteplase (Intravenous – ischaemic stroke) Drug Guideline (DRG0013).

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 with haemodynamic compromise (massive pulmonary embolism).
- Pulmonary embolism without 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

Absolute contraindications
- Active bleeding or bleeding diathesis (excluding menses).
- Significant closed head or facial trauma within 3 months.
- Suspected aortic dissection (including new neurological symptoms).
- Any prior intracranial haemorrhage.
- Ischaemic stroke within 3 months.
- Known structural cerebral vascular lesion (e.g. arteriovenous malformation).
- Known malignant intracranial neoplasm (primary or metastatic).
Relative contraindications:
- Current use of anticoagulants. With warfarin the higher the international normalised ratio (INR), the higher the risk of bleeding.
- Recent non-compressible vascular punctures, obstetric delivery or organ biopsy (within 10 days).
- Recent major surgery (within 3 weeks).
- Traumatic or prolonged (greater than 10 minutes) cardiopulmonary resuscitation.
- 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, greater than 110 mmHg diastolic)
- Ischaemic stroke greater than 3 months ago, dementia, or known intracranial abnormality not covered in absolute contraindications
- Pregnancy – 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 (abciximab, 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 post alteplase administration before performing any of these procedures.
- **See Nursing Practice Points for a range of Precautions** that apply during alteplase administration and for the next 12-24 hours.

PREGNANCY AND BREASTFEEDING
Seek specialist advice before prescribing, information may update regularly.
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:

<table>
<thead>
<tr>
<th>Other thrombolytics</th>
<th>reteplase, tenecteplase, urokinase.</th>
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</thead>
<tbody>
<tr>
<td>Heparin and low molecular weight heparins</td>
<td>dalteparin, danaparoid, enoxaparin, heparin.</td>
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<tr>
<td>Direct thrombin inhibitors</td>
<td>bivalirudin, dabigatran</td>
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<tr>
<td>Vitamin K antagonists</td>
<td>warfarin.</td>
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<tr>
<td>Factor Xa inhibitors</td>
<td>apixaban, fondaparinux, rivaroxaban.</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>abciximab, eptifibatide, tirofiban.</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory agents</td>
<td>Aspirin (low dose if indicated OK), diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, naproxen, piroxicam, sulindac. Note: Selective NSAIDs (celecoxib, etoricoxib, meloxicam, parecoxib) do not directly affect clotting, but increase the risk of gastrointestinal bleeding</td>
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<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline</td>
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<tr>
<td>Prostacyclin analogues</td>
<td>epoprostenol, iloprost, treprostinil.</td>
</tr>
<tr>
<td>Other</td>
<td>anagrelide, cilostazol, clopidogrel, dipyridamole, drotecogin alpha (within 3 days), prasugrel, protein C concentrate (human), ticagrelor, ticlopidine.</td>
</tr>
<tr>
<td>Herbal medications</td>
<td>Alfalfa, anise, bilberry, bladderwrack, bromelain, cat’s claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (american), ginseng (panax), ginseng (siberian), grape seed, green tea, guggul, horse chestnuts, horseradish, licorice, prickly ash, red clover, reishi, S-adenosylmethionine, sweet clover, turmeric, white willow</td>
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</table>

- 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 reoclusion. Use the lowest dose of glyceryl trinitrate possible.
- Aprotinin - may decrease the therapeutic effect of alteplase.
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 under the supervision of a Consultant. Contraindications and Precautions above MUST be reviewed prior to prescribing, and consent obtained from patient/family where possible.

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

The total dose of alteplase (variable by weight) is split and administered as an IV loading (bolus) dose (10 mg), followed IMMEDIATELY by an IV infusion (variable by weight) over 2 hours. Ensure both loading (bolus) dose and infusion are prepared prior to commencing alteplase. Depending on the dose required, the 10 mg load can be taken from the 10 mg vial or the 50 mg – see table below re vial selection.

Any patient that may be a candidate for thrombolysis of pulmonary embolism should be started on a heparin infusion (as per Heparin Drug Guideline – DRG0038) during assessment. Heparin is then suspended during alteplase administration, and restarted after alteplase administration once the APTT is less than twice the upper limit of normal. Low molecular weight heparins and novel oral anticoagulants (NOACs) are not appropriate during this acute phase due to a lack of reversibility. Note: heparin is incompatible with alteplase, and must be given via a different line, 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, NOACs during or 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 imprest alteplase must be stored separate to other thrombolitics with a sign stating 'For thrombolysis of STROKE or Pulmonary Embolism ONLY'.

Administer via CVC, midline or peripheral line. Administer via a dedicated line, do not mix with any other drugs or fluids.

1.) Determine dose to be administered and prescribe:

See Appendix 1 ‘Alteplase in Pulmonary Embolism Flowchart’ also.

All alteplase doses are to be prescribed by the ED, ICU or Medical Registrar under the supervision of a Consultant. Maximum total dose 100 mg including loading dose.

- If 65 kg or greater: 10 mg loading dose IV over 1 minute, then 90 mg IV infusion over 2 hours.
- If less than 65 kg: maximum 1.5 mg/kg with 10 mg loading dose IV over 1 minute, and remainder of dose by IV infusion over 2 hours (e.g. 50 kg patient = max 75 mg given as 10 mg load and then 65 mg over 2 hours).

Prescribe as:

Alteplase 10 mg undiluted IV over ONE minute, immediately followed by

Alteplase X mg diluted to 100 mL sodium chloride 0.9% IV over TWO hours.

(X represent the calculated dose required)
2.) Vial selection:
Alteplase is very expensive (around $1810 per 50 mg vial and $535 per 10 mg vial), as such wastage is to be avoided. Vials are to be selected based on dose as outlined in the table below, and not reconstituted until it is certain that alteplase is to be given.

<table>
<thead>
<tr>
<th>ALTEPLASE Total Dose (max 100 mg)</th>
<th>Number of vials required to obtain calculated dose from</th>
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</thead>
<tbody>
<tr>
<td>51-60 mg</td>
<td>50 mg vial x1 and 10 mg vial x1</td>
</tr>
<tr>
<td>61-70 mg</td>
<td>50 mg vial x1 and 10 mg vial x2</td>
</tr>
<tr>
<td>71-80 mg</td>
<td>50 mg vial x1 and 10 mg vial x3</td>
</tr>
<tr>
<td>81-100 mg</td>
<td>50 mg vial x2</td>
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3.) Vial reconstitution:
Reconstitute each alteplase 10 mg vial required with 10 mL of diluent (preservative free water for injection supplied with alteplase). This gives a 1 mg/mL solution.
Reconstitute each alteplase 50 mg vial required with 50 mL of diluent (preservative free water for injection supplied with alteplase). This gives a 1 mg/mL solution.

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 BY NURSING STAFF

4.) Prepare loading (bolus) dose and infusion:
The infusion commences IMMEDIATELY after the loading (bolus) dose has finished, as such both doses must be drawn up and ready to commence at the same time.

Load: Draw the loading (bolus) dose of 10 mg (10 mL) up in a 10mL syringe and attach an additive label. Do not dilute further.

Infusion: Withdraw and discard from a sodium chloride 0.9% 100 mL minibag the same volume that is required of alteplase for the infusion. Draw up the required infusion dose in one or two 50 mL syringes and ADD the dose to the minibag for a final volume of 100 mL. Attach an additive label.

5.) Confirm with Medical staff that heparin infusion is to be suspended during alteplase infusion:
6.) **Administer IV loading (bolus) dose IMMEDIATELY prior to infusion:**
Alteplase 10 mg undiluted by IV injection over 1 minute.

7.) **Administer IV infusion IMMEDIATELY after loading dose:**
Alteplase dose (as calculated above) diluted to 100 mL in sodium chloride 0.9% minibag and administer by IV infusion over 2 hours (50 mL/hr).

Use the alteplase solution to prime the line. Administer via Alaris PC pump with LVP using Guardrails (select Alteplase, then Pulmon Emboli 65kg+ or Pulmon Emboli <65 kg).

At the completion of the infusion, flush the line with 30 mL of sodium chloride 0.9% at 50 mL/hr.

8.) **Confirm with Medical staff when heparin infusion is to recommence:**
Once the initial haemostatic defect has partly resolved (repeat APPT immediately once alteplase infusion has finished), with the APTT less than twice the upper limit of normal, restart the heparin infusion as per the Heparin Drug Guideline (DRG0038) or ‘Heparin Intravenous Infusion Chart’ (MR/700.3).

**General Administration Information**
- **Infusion pump:** Alaris PC pump with LVP using Guardrails
- **Routes of administration:**
  - IV injection:
  - IV intermittent infusion:
  - IV continuous infusion:
  - IM injection:
  - Subcut injection:
- **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, 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 any signs of bleeding are detected** during alteplase administration, cease alteplase and 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:** as outlined in the Thrombolysis for Acute Ischaemic Stroke (CPP0012) – During and After Administration of Alteplase and Thrombolysis in Acute Ischaemic Stroke Pathway (MR/265.05).
- Monitor continuously for signs of internal bleeding (tachycardia, hypotension, pallor, restlessness, lower back pain, new muscle weakness/numbness in lower extremities).
- Assess for external bleeding (e.g. IV sites, gums) hourly.
- Urine full ward test each void or 6/24 for indwelling catheter.
- Faecal occult blood test.
- Blood pressure (with manual blood pressure cuffs to avoid bruising from over-inflation from automatic blood pressure machines), HR, RR, SaO2, temp and GCS every 15 minutes during the infusion and every 30 minutes thereafter for the next 6 hours, then hourly until 24 hours after treatment. A change in 2 points of GCS should be reported to the ED/ICU/Medical Registrar immediately.
- Strict maintenance of fluid balance chart.

**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), new oral anticoagulants or warfarin.
- Venepuncture must only be undertaken as outlined in the Thrombolysis for Acute Ischaemic Stroke (CPP0012) – Post Administration of Alteplase section.
- 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.
- If required, supplemental oxygen must be administered via a mask as nasal prongs can cause nasal mucosa damage.
- Falls prevention.
- Use only electric shavers.
- All injections and infusions are to be labelled as per CPP0022 Labelling of Injectable Medicines and Lines.

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**ADVERSE EFFECTS**

- **Serious bleeding** – 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.

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**DRUG PRESENTATIONS, LOCATION AND STORAGE**

Alteplase 10 mg and 50 mg vials.

Store below 30°C. Protect vials from light.
ALTEPLASE in Massive Pulmonary Embolism Flowchart

Review: Pulmonary Embolism – Diagnosis and Initial Management of Patients with suspected Pulmonary Embolism (CPG0087) and Alteplase (Intravenous – pulmonary embolism) (DRG 0052) prior to prescribing ALTEPLASE and for more information.

All ALTEPLASE doses are to be prescribed by the ED, ICU or Medical Registrar under the supervision of a Consultant. Maximum total dose 100 mg including loading dose.

Dose:
- If 65 kg or greater: 10 mg loading dose IV over 1 minute, then 90 mg IV infusion over 2 hours.
- If less than 65 kg: maximum 1.5 mg/kg with 10 mg loading dose IV over 1 minute, and 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).

Prescribe as: ALTEPLASE 10 mg undiluted IV over ONE minute, immediately followed by ALTEPLASE X mg diluted to 100 mL sodium chloride 0.9% IV over TWO hours. (X represents the calculated dose required)

ALL DOSES REQUIRE AN INDEPENDENT DOUBLE CHECK BY NURSING STAFF

Select number of vials required to administer dose using the table in DRG0052

Reconstitute the required vials using the WFI diluent provided with the vials to make a 1 mg/mL solution. Use the information provided in the box. Swirl gently, DO NOT SHAKE.

Prepare loading dose and infusion sequentially, with both prepared before dosing commences

Load: Draw the loading (bolus) dose of 10 mg up in a 10mL syringe and attach an additive label. Do not dilute further.

Infusion: Withdraw and discard from a sodium chloride 0.9% 100 mL minibag the same volume that is required of ALTEPLASE for the infusion. Draw up the required infusion dose in one or two 50 mL syringes and ADD the dose to the minibag for a final volume of 100 mL. Attach an additive label.

Administer IV loading dose IMMEDIATELY prior to infusion: ALTEPLASE 10 mg undiluted by IV injection over 1 minute.

Administer IV infusion IMMEDIATELY after loading dose via Alaris PC pump with LVP using Guardrails (select Alteplase, then Pulmon Emboli 65kg+ or Pulmon Emboli <65 kg):

Use the ALTEPLASE solution to prime the line.
ALTEPLASE dose (as above) diluted to 100 mL in sodium chloride 0.9% minibag and administer by IV infusion over 2 hours (50 mL/hr).
At the completion of the infusion, flush the line with 30 mL of sodium chloride 0.9% at 50 mL/hr.

Once the APTT less than twice the upper limit of normal, restart heparin infusion (with no load) as per the Heparin Drug Guideline (DRG0038) or ‘Heparin Intravenous Infusion Chart’ (MR/700.3).