Gloucestershire Hospitals
NHS Foundation Trust

Rapid Trust-wide Guidelines

Thrombolytic options in view of global Alteplase shortage

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1. INTRODUCTION

The National Patient Safety Alerting Committee have issued a National Patient Safety Alert titled "Shortage of alteplase and Tenecteplase injections" – NatPSA/2022/006/DHSC on 3rd August 2022. There will be supply constraints facing alteplase (Actilyse®) 10mg, 20mg and 50mg injections for the remainder of 2022. Tenecteplase (Metalyse®) 10,000unit injections will go out of stock in the coming months. At present the situation is expected to improve in early 2023.

Alteplase is licensed for thrombolytic treatment of acute ischaemic stroke, acute myocardial infarction (MI) and acute massive pulmonary embolism (PE) with haemodynamic instability. Tenecteplase is licensed for the management of acute MI.

Boehringer Ingelheim is the sole supplier of both these products in the UK. There are manufacturing constraints causing global issues with the supply of these products.

With the above in mind, through rapid dissemination of information and completing the actions outlined in the NPSA alert, this guideline has been developed to help with dosing and administration of thrombolytics.

2. INDICATIONS and agents as agreed across specialities in response to Alert

Indication	First-line agent
Acute Ischaemic Stroke	**Alteplase**
Massive PE	Streptokinase *instead of alteplase*
Pleural Infection	Urokinase *instead of alteplase*
Limb threatening ischaemia	Urokinase *instead of alteplase*
Acute STEMI where PPCI unavailable	PPCI service now 24/7/365

Where patients are ineligible for the first line therapies, a multi-disciplinary discussion must be undertaken including Medicines Safety Officer or a senior pharmacist to discuss and agree use of any alternative thrombolytic agent. The outcome of these discussions and decision made should be recorded on Datix for monitoring of deviation from this guideline.

3. ALTEPLASE

Alteplase must be reserved for acute ischaemic stroke.

Stock will not be centralised to pharmacy but will be kept in locations within the Trust where stroke treatment is administered.

Due to the lack of stock, vial selection is important to minimise wastage. Trust guidelines should be followed but vial selection should be considered:

Alteplase Vial Selection

Estimate of Patients weight (kg)	Equivalent Imperial Weight	Total Dose (mg at 1mg/ml)	Vials needed to make up Total dose			Bolus dose (mls) over 1-2mins	Infusion dose (mls) = infusion rate in mls/hr
			50mg	20mg	10mg		
45	7 st 1 lb	40	1	0	0	4.0	36.0
50	7 st 12 lb	45	1	0	0	4.5	40.5
55	8 st 9 lb	49	1	0	0	4.9	44.1
60	9 st 6 lb	54	1	0	1	5.4	48.6
65	10 st 3 lb	58	1	0	1	5.8	52.2
70	11 st 0 lb	63	1	1	0	6.3	56.7
75	11 st 11 lb	67	1	1	0	6.7	60.3
80	12 st 8 lb	72	2	0	0	7.2	64.8
85	13 st 5 lb	76	2	0	0	7.6	68.4
90	14 st 2 lb	81	2	0	0	8.1	72.9
95	14 st 13 lb	85	2	0	0	8.5	76.5
≥100	15 st 10 lb	90	2	0	0	9.0	81.0

4. STREPTOKINASE

Thrombolysis for massive pulmonary embolism
A0365: Thrombolysis for Massive Pulmonary Embolism Guideline (gloshospitals.nhs.uk)
Streptokinase should be used instead of alteplase recommended in the above guideline.
Dose: Give hydrocortisone 100mg by intravenous injection to reduce the likelihood of infusion-related allergic reactions, **then** infuse 1,500,000 units of streptokinase into a peripheral vein over 1-2 hours.
Note: In the unlikely event that the patient has received streptokinase within the last 12 months, give alteplase as per above guideline.

5. UROKINASE

Intrapleural fibrinolytics for pleural infection (unlicensed indication)
Intrapleural Fibrinolytics for Pleural Infection (gloshospitals.nhs.uk)
Urokinase should be used instead of alteplase recommended in the above guideline. Decision to treat must be made by a respiratory consultant and patients should have daily consultant review.
Dose: 100,000 units in 30ml sodium chloride 0.9% intrapleurally twice daily (alongside dornase alfa 5mg) for a maximum of 3 days.

Limb threatening ischaemia

> **Acute occlusive peripheral arterial disease with limb threatening ischaemia**
>
> A solution of 2,000 IU/ml (500,000 IU Syner-KINASE® dissolved in 250 ml solvent) should be infused into the clot with angiographic monitoring of progress of treatment. It is recommended that the rate of infusion should be 4,000 IU/minute for 2 hours when angiography should be repeated. Following this, the catheter should be advanced into the occluded segment of vessel and Syner-KINASE® infused at the same rate of 4,000 IU/minute for another 2 hours. The process can be repeated up to 4 times if flow has not been achieved. Once a channel has been created through the blocked segment, the catheter may be withdrawn until it lies proximal to the remaining thrombus. Infusion should continue at the rate of 1,000 IU/minute until the clot has completely lysed. Usually, a dose of 500,000 IU over 8 hours should be sufficient. If the length of the clot has not been reduced by more than 25% after the initial dose of 500,000 IU and further reductions of 10% by subsequent infusions of 500,000 IU, discontinuation of treatment should be considered.

6. REFERENCES

- National Patient Safety Alerting Committee, 2022. Shortage of alteplase and Tenecteplase injection available via: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103211
- BTS: https://www.brit-thoracic.org.uk/news/2022/bts-response-to-the-national-shortage-of-alteplase-in-relation-to-pleural-infection-management/
- SPC: Streptokinase. https://www.medicines.org.uk/emc/product/13114/smpc
- SPC: Syner-KINASE (urokinase) 100,000 IU powder for solution for injection/infusion. Available from: https://www.medicines.org.uk/emc/product/7565/smpc

APPENDIX 1

National Patient Safety Alert

Department of Health & Social Care | NHS England

Shortage of alteplase and tenecteplase injections

Date of issue:	3-Aug-22	Reference no:	NatPSA/2022/006/DHSC
This alert is for action by: All organisations using alteplase and tenecteplase injections			
This is a safety critical and complex National Patient Safety Alert. Implementation should be co-ordinated by an executive lead (or equivalent role in organisations without executive boards) and supported by the Pharmacy department and clinical leaders in stroke medicine, respiratory medicine, renal, cardiology, and emergency medicine.			

Explanation of identified safety issue:

There will be supply constraints facing alteplase (Actilyse®) 10mg, 20mg and 50mg injections for the remainder of 2022. Tenecteplase (Metalyse®) 10,000unit injections will go out of stock in the coming months. At present the situation is expected to improve in early 2023.

Alteplase is licensed for thrombolytic treatment of acute ischaemic stroke, acute myocardial infarction (MI) and acute massive pulmonary embolism (PE) with haemodynamic instability. Tenecteplase is licensed for the management of acute MI.

Boehringer Ingelheim is the sole supplier of both these products in the UK. There are manufacturing constraints causing global issues with the supply of these products.

Availability of stock

Boehringer Ingelheim has put restrictions in place for alteplase injection to conserve supplies until further stock is available. Trusts will have access to:

- Alteplase 50mg – approximately normal demand
- Alteplase 20mg – approximately half of normal demand
- Alteplase 10mg – approximately two thirds of normal demand

Demand is calculated at trust level based on historical orders and stock available in trusts and will be coordinated by Boehringer Ingelheim and the Regional Pharmacy Procurement Specialists.

Boehringer Ingelheim has also put restrictions in place for tenecteplase to ensure stock is not depleted earlier than anticipated.

Actions required

Actions to be completed by
10/08/2022

1. Assess stock holding of alteplase and tenecteplase injections to ensure current stock levels are correctly recorded in pharmacy systems.
2. Centralise stock in pharmacy where appropriate to do so.
3. Alteplase stock should be conserved for patients with acute ischaemic stroke, given the lack of an alternative and the significant risk of harm without receipt of treatment.
4. Consider the feasibility of alternative therapeutic options to alteplase and tenecteplase where they exist.
5. Reduce wastage by selecting appropriate vial sizes and using the most appropriate doses, giving consideration to rounding down to the nearest whole vial.
6. Pharmacy staff should order alteplase injections in line with their allocations and order tenecteplase injection in line with historic order patterns; unusual orders will be challenged.
7. Pharmacy staff should liaise with their Regional Pharmacy Procurement Specialist to manage allocated stocks of alteplase. Ensuring proactive stock management and prompt liaison should stock levels become critically low.

For any enquiries about this alert contact: DHSCmedicinesupplyteam@dhsc.gov.uk 1/2

Failure to take the actions required under this National Patient Safety Alert may lead to CQC taking regulatory action

Additional information:

Alternative thrombolytic treatments

Stroke

Only alteplase is licensed for the treatment of ischaemic stroke. Stroke teams may also have experience of using tenecteplase from participation in clinical trials, though this would be an unlicensed use. Mechanical thrombectomy is also used to treat some patients with acute ischaemic stroke but should be used in conjunction with alteplase in the majority of patients. There are no other therapeutic options for the treatment of acute ischaemic stroke.

Myocardial Infarction and dissolution of thrombi and emboli

Streptokinase

- The 1,500,000 IU strength is licensed for the treatment of acute MI within 12 hours of onset with persistent ST-segment elevation or recent left bundle-branch block.
- The 250,000 and 750,000 IU strengths are licensed for intravascular dissolution of thrombi and emboli in: acute massive pulmonary embolism, acute, sub-acute or chronic (not older than 6 weeks) occlusion of peripheral arteries, extensive deep vein thrombosis, and central retinal venous or arterial thrombosis (arterial occlusions not older than 8 hours, venous occlusions not older than 10 days).

Repeat treatment with streptokinase administered more than 5 days and less than 12 months after initial treatment may not be effective due to increased likelihood of resistance as a result of antistreptokinase antibodies. Also, the therapeutic effect may be reduced in patients with recent streptococcal infections such as streptococcal pharyngitis, acute rheumatic fever and acute glomerulonephritis.

Urokinase

Urokinase is licensed for:

- thrombosed intravascular catheters and cannulae,
- extensive acute proximal deep vein thrombosis,
- acute massive pulmonary embolism, and
- acute occlusive peripheral arterial disease with limb threatening ischaemia

Supplies of urokinase 10,000 units and 25,000 units are not available however, urokinase 100,000 units is meeting demand and can support a small increase in use; please refer to the Medicine Supply Notification which includes link to Dear HCP letter regarding dilution of this high strength product.

Off label uses

For the thrombolytic treatment of occluded central venous access devices including those used for haemodialysis; please refer to Medicine Supply Notification the issued for the shortage of alteplase (Actilyse Cathflo®) 2mg powder for solution for injection vials. For paediatric use, alteplase should only be used as rescue therapy to preserve vascular access in children on haemodialysis when other agents have been ineffective. For prophylaxis of central venous line occlusion in paediatrics, alteplase should only be used for the highest risk patients i.e. infants and small children.
For other off label uses, discuss locally with the relevant specialist noting the advice contained within this alert.

References

SmPC alteplase
SmPC tenecteplase
SmPC streptokinase
SmPC urokinase
NICE guideline for stroke and transient ischaemic attack in over 16s: diagnosis and initial management
NICE guidelines for management of acute coronary syndromes
NICE guideline for the diagnosis and management of atrial fibrillation

Stakeholder engagement

The following stakeholders have been engaged in the management and consulted in the drafting of this alert: Specialist Pharmacy Service Medicines Information, Medicine Shortage Response Group, NHS England National Clinical Directors for stroke, heart disease and respiratory, and specialist renal clinicians.

Advice for Central Alerting System (CAS) officers and risk managers

This is a safety critical and complex National Patient Safety Alert. In response to CHT/2019/001 your organisation should have developed new processes to ensure appropriate oversight and co-ordination of all National Patient Safety Alerts. CAS officers should send this Alert to the executive lead nominated in their new process to coordinate implementation of safety critical and complex National Patient Safety Alerts, copying in the leads identified on page 1.