South East London Area Prescribing Committee
Formulary recommendation

Reference	**042**
Intervention:	**Alteplase for the treatment of acute massive and sub-massive pulmonary embolus** (Alteplase is a recombinant tissue-type plasminogen activator thrombolytic agent which degrades fibrin and breaks down clots)
Date of Decision	**November 2015**
Date of Issue:	**December 2015**
Recommendation:	**RED – suitable for prescribing and supply by hospital only**
Further Information	**Massive pulmonary embolus (PE)** • Alteplase is supported for use in the treatment of massive pulmonary embolus (PE) and sub-massive PE. • The use of alteplase 100mg for the treatment of massive PE (haemodynamically unstable) is licensed and is accepted practice in the UK.
	Sub-massive PE • Sub-massive PE is a hameodynamically stable PE which presents with circulatory collapse, arrthythmia, hypovolaemia or sepsis and there is evidence of right heart strain and/or myocardial injury. • Alteplase is not licensed for the treatment of sub-massive PE but is used in a low dose regimen in this indication. Patients will need to be informed of the unlicensed nature in line with the organisation's usual consent processes. • Alteplase treatment is administered as a single dose by intravenous injection. • Approval is granted on the condition that Trusts develop robust in-house guidelines for the management of massive and sub-massive PE and that these are approved through their Drug and Therapeutic Committees (or equivalent). • In particular, where Trusts decide to adopt the use of alteplase in sub-massive PE – this is highly specialist and appropriate governance should be in place to enable safe use of the drug in this setting. This should include a requirement that a minimum of 2 consultants will be involved in making an informed decision on the suitability of alteplase treatment on a case by case basis.
	Tariff arrangements for alteplase At time of writing, alteplase is a tariff excluded, CCG commissioned drug. However, a consultation on national tariff arrangements for 16/17 is underway. This has proposed that alteplase is no longer tariff excluded (i.e. becomes in-tariff). In view of this, funding will need to be confirmed at individual Trust level from April 2016 onwards if alteplase is no longer tariff excluded in the final published National Tariff guidance for 16/17.
Shared Care/ Transfer of care required:	N/A
Cost Impact for agreed patient group	• The cost of treating massive PE with alteplase (100mg) is £864 per patient. • PE has an incidence of 30-40 per 100,000 population, with 10% presenting haemodynamically unstable PE. If treated with alteplase, this equates to a cost of approximately £2,500 per 100,000 population. • The application to the APC suggests the sub-massive PE cohort would approximately be the same size as the massive PE cohort. This would result in a cost of approximately £1,250 per 100,000 population.

Usage Monitoring & Impact Assessment	Acute Trusts: • Monitor usage and report back to APC when required. • Develop in house Trust guidelines and audit against these guidelines as required by the APC.
	CCGs: • Monitor monthly tariff excluded high cost drugs invoicing submitted by Trusts to the South East CSU
Evidence reviewed	**References (from evidence review)** 1. Camm, A.J. and Bunce, N.H. (2005) Cardiovascular disease. In: Kumar, P. and Clark, M. (Eds.) *Kumar & Clark Clinical Medicine*. 6th edn. London: Elsevier Saunders. 725-871. 2. Tapson, V.F. (2008) Acute pulmonary embolism. *New England Journal of Medicine* 358(10), 1037-1052 3. Torbicki, A., Perrier, A., Konstantinides, S. et al. (2008) Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *European Heart Journal* 29(18), 2276-2315 4. Huerta, C., Johansson, S., Wallander, M.A. and Garcia Rodriguez, L.A. (2007) Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. *Archives of Internal Medicine* 167(9), 935-943 5. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing Clinical Guideline 144, The National Institute for Health and Care Excellence 2012 6. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest. 2002; 121(3):877-905. 7. Kucher, N., Rossi, E., De Rosa, M. and Goldhaber, S.Z. (2006) Massive pulmonary embolism. *Circulation* **113**(4), 577-582 8. Jaff M, McMurty M, Archer S et al. Management of massive and submassive pulmonary embolism, ileofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011; 123 p1788-1830 9. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999; 353(9162):1386-1389. (Guideline Ref ID GOLDHABER1999) 10. The British National Formulary 70th Edition, September 2015. 11. Actilyse, Summary of Product Characteristics, [accessed on 06/11/2015] 12. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism, Technology Appraisal 329, NICE 2014 13. Rivaroxaban for the treatment of Pulmonary embolism and preventing recurrent venous thromboembolism, Technology Appraisal 287, NICE 2013 14. Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism, Technology Appraisal 341, NICE 2015 15. Edoxaban etexilate for treating and for preventing deep vein thrombosis and pulmonary embolism, Technology Appraisal 354, NICE 2015 16. Sharifi M, Bay C, Skrocki L. Moderate Pulmonary Embolism Treated with Thrombolysis (from the "MOPETT" Trial. American Journal of Cardiology 2013 **111** p273-277. 17. British Thoracic Society Guidelines for the Management of Suspected Acute Pulmonary Embolism. Thorax 2003 **58** p470-484. 18. Fasullo S, Scalzo S, Maringhini G, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. American Journal of Medical Science. 2011; 341 **1** p33-39. 19. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014; 129 **4** p479-486. 20. Meyer G, Vicaut E, Danays T, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. New England Journal of Medicine. 2014; 370 **15** p1402-1411. 21. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: A Meta-analysis. Journal of the American Medical Association. 2014; 311 **23** p2414-2421 22. Perlroth DJ, Sanders GD, Gould MK. Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism. Archives of Internal Medicine. 2007; 167 **1** p74-80 23. Kanter D, Mikkola K, Patel S et al. arker JA, Goldhaber SZ. Thrombolytic therapy for pulmonary embolism: frequency of intracranial hemorrhage and associated risk factors. Chest 1997 **111** p1241-5 24. Levine MN. Thrombolytic therapy for venous thromboembolism: complications and contraindications. Clinics in Chest Medicine 1995 **16** p321-8.

NOTES:

a) Area Prescribing Committee recommendations and minutes are available publicly on member CCG websites.

b) This Area Prescribing Committee recommendation has been made on the cost effectiveness, patient outcome and safety data available at the time. The recommendation will be subject to review if new data becomes available, costs are higher than expected or new NICE guidelines or technology appraisals are issued.

c) **Not to be used for commercial or marketing purposes. Strictly for use within the NHS.**