AWMSG Secretariat Assessment Report – Advice no. 1911
Alteplase (Actilyse® Cathflo® 2 mg) powder and solvent for injection and infusion

This assessment report is based on evidence from a limited submission by Boehringer Ingelheim Ltd on 11 July 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Alteplase (Actilyse® Cathflo® 2 mg) is indicated for thrombolytic treatment of occluded central venous access devices including those used for haemodialysis[1].
Dosing	Actilyse® Cathflo® 2 mg should be given as soon as possible after symptom onset. A dose of up to 2 mg, administered up to two times for any one occlusion, can be used to restore function of ports and single and multiple lumen catheters, including those used for haemodialysis, which became dysfunctional due to thrombotic occlusion. For use in this indication, reconstitution to a final concentration of 1 mg alteplase per ml is recommended. If function is not restored 120 minutes after the first dose, a second dose of equal amount may be instilled[1]. Refer to the Summary of Product Characteristics (SPC) for dosing for specific body weights and for method of catheter clearance[1].
Marketing authorisation date	29 November 2010[1].

2.0 DECISION CONTEXT

2.1 Background

Central venous access devices (CVADs) are important for maintaining consistent infusion of medication, blood products and parenteral nutrition, as well as for extraction of blood products/samples and waste (haemodialysis)[2–5]. A 1993 report estimated that 200,000 CVADs are placed in the UK annually[6]. Occlusion of a CVAD is associated with increased morbidity and mortality[7] due to complications such as venous stasis, enhanced coagulability, vessel wall trauma, and infection[2,8,9]. Estimates state that 14–36% of CVADs will become occluded within 1–2 years of placement[10–17], the most common cause being thrombosis[2,13,14], which occurs in up to 50% of children and 66% of adults with a long-term CVAD[2]. Where thrombotic obstruction is suspected, pharmacologic management with a thrombolytic agent is considered[7].

Alteplase is a recombinant human tissue-type plasminogen activator (t-PA) which dissolves fibrin clots. When bound to fibrin, it is activated, inducing the conversion of plasminogen to plasmin, leading to dissolution of the clot. The alteplase 2 mg vial (Actilyse® Cathflo® 2 mg) is currently the only presentation of alteplase licensed for use in this indication. Once reconstituted, Actilyse® Cathflo® 2 mg is intended for direct injection into a thrombotically occluded CVAD[1].

2.2 Comparators
The applicant company, in agreement with the Welsh Medicines Partnership (WMP), have used urokinase as the comparator.

2.3 Guidance and related advice
- Bishop L, Dougherty L, Bodenham A et al. Guidelines on the insertion and management of central venous access devices in adults. 2007[18].
- Baskin JL, Pui CH, Reiss U et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. 2009[2].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Clinical effectiveness evidence
The company submission described two published head-to-head studies comparing alteplase and urokinase[7,10], in addition to a phase III, placebo-controlled clinical trial of alteplase (A2055g [COOL-1]), for restoring CVAD function after thrombotic occlusion. The company submission also included two studies which focussed on safety: A2065g (COOL-2; a phase III clinical trial)[3] and A2404g (Cathflo® Activase® [alteplase] paediatric study [CAPS]; a phase IV clinical trial)[19]. Supportive safety data from a phase II trial of recombinant urokinase (r-UK) was also provided[20].

3.1.1 Comparative studies
Haire et al (1994) published the results of a prospective, randomised, double-blind comparison of alteplase 2 mg/2 ml and urokinase (10,000 IU/2 ml). CVAD function was measured as the primary endpoint of the study. Fifty CVADs with radiographically proven thrombotic occlusion in forty-eight oncology patients (aged > 19 years) were randomised to alteplase (n = 28) or urokinase (n = 22). The study drug was injected into the CVAD and left for 120 minutes, at which point attempts were made to withdraw and infuse through the CVAD. If normal function was not restored, a second dose was permitted. Function was restored in significantly more CVADs treated with alteplase than urokinase (25/28 [89%] versus 13/22 [59%], respectively, p = 0.013). No complications were observed in either group[10].

A small, retrospective review of haemodialysis patients with CVADs at a single US site by Eyrich et al (2002) found that of 27 patients who received 1 ml alteplase (1 mg/ml) and 10 patients who received 5,000 IU/ml urokinase for presumed thrombosis, 70% versus 35%, respectively, achieved restored haemodialysis blood flow (p = 0.0134).

COOL-1 (a multicentre, randomised, double-blind, placebo-controlled phase III trial) was designed to confirm the results reported by Haire et al, but without administering X-ray contrast injection[3]. Subjects (≥ 2 years of age) with occluded, non-dialysis CVADs were enrolled from 36 US sites[21]. Patients were excluded if they were at high risk of bleeding events or had recent embolic complications. The study was designed to allow each patient to be treated with both placebo and alteplase; patients (n = 149) were randomised 1:1 to one of two arms: in one arm (n = 75), the first two vials contained alteplase (2 mg/2 ml) and the third contained placebo; in the other (n = 74), the first vial contained placebo and the following two contained alteplase (2 mg/2 ml). After administration of the first vial, CVADs which remained dysfunctional at 120 minutes received the second vial, followed by the third where required. After the first 120-minute period, restoration of function was seen in significantly more alteplase-treated CVADs than placebo-treated CVADs (51/69 [73.9%] versus 12/70 [17.1%], respectively, p < 0.0001). In each arm, the second dose was alteplase, after which restoration in function was seen in 124/138 (89.9%) of patients. No adverse events (AEs) or treatment-related deaths or discontinuations were reported[21].

3.1.2 Comparative safety

COOL-2 was a multicentre, open-label, single-arm phase III trial which evaluated the safety and efficacy of alteplase in 995 patients (aged 2–91 years) from 78 US centres with occluded, non-dialysis CVADs (contrast injection study was not performed). Patients were excluded if they were at high risk of bleeding events or embolic complications. All patients received 2 mg/2 ml alteplase, and CVADs which remained dysfunctional at 120 minutes received a second dose. The primary endpoint of COOL-2 was the safety of serial administration of up to two doses of alteplase; the primary safety outcome measured was the proportion of patients with intracranial haemorrhage (ICH) within five days of treatment. No patient experienced ICH during the study. There were three cases of major haemorrhage (0.3%; 95% confidence interval [CI], 0.1–0.9%) within five days of treatment; however, none of these were interpreted as treatment-related. Three subjects (0.3%) experienced AEs (sepsis) that were possibly related to study treatment, one case of which was serious, leading to withdrawal. There was no correlation between AEs and total dose of alteplase received. No treatment-related deaths were reported[3].

CAPS was an open-label, single-arm, multicentre phase IV trial conducted at 42 sites in the US to extend the safety data in the paediatric population. Patients (n = 310, ≤ 16 years of age) were treated with up to two doses of alteplase (≤ 2 mg/ 2 ml). Incidence of ICH and occurrence of specific targeted serious AEs (SAEs: major haemorrhage, thrombosis, embolic events, sepsis and catheter-related complications) at any time during the treatment period, or within 48–96 hours of treatment completion, were measured as the primary and secondary endpoints, respectively. No patients experienced ICH. Nine SAEs were noted in eight patients (2.6%), two of which were attributed to study drug: one case of sepsis and one case of a ruptured catheter lumen[19].

The company submission also included details of a phase II, double-blind, placebo-controlled trial detailing the safety of urokinase (5,000 IU/ml, 15,000 IU/ml and 25,000 IU/ml). Of 108 patients randomised, treatment-related haemorrhagic events occurring within 72 hours were experienced by four patients (17%) in the 25,000 IU/ml group, two patients (7%) in the 15,000 IU/ml group, no patients in the 5,000 IU/ml group, and no patients in the placebo group[20,22].

3.2 WMP critique

- The 1994 study by Haire et al noted that making no attempts to prove catheter dysfunction was due to thrombus (as opposed to malposition or other mechanical problem) was a significant limitation, and therefore performed radiographic contrast studies to confirm the presence of a thrombus[10]. However, Deitcher et al (2002) considered the requirement for a radiologist to inject a CVAD with contrast and radiographically confirm the presence of a clot to be a limitation[3]. Therefore, trials COOL-1 and COOL-2 assumed thrombotic occlusion with no contrast injection study[3,21]. As a consequence, it was acknowledged that no conclusions could be reached as to the efficacy of restoration of flow based on the cause of catheter malfunction[21].
- Few data are provided for the use of alteplase in haemodialysis CVADs. The retrospective review by Eyrich et al (2002) was the only study to predominantly consider haemodialysis CVADs, but only 37 patients were included in the final analysis. Additionally, this study did not use the recommended dose of alteplase, allowed investigator choice of treatment and did not perform contrast injection study[7].
- The comparative study by Haire et al (1994) used the dose of alteplase recommended by the SPC (2 mg/2 ml)[1], but only used the minimum dose of

urokinase recommended by the SPC (5,000 IU/ml)[10,23]. This precludes confirmation of superiority of alteplase across the full dosing range for urokinase (5,000–25,000 IU/ml). The phase II clinical trial published by Deitcher et al (2004) was the only study provided in which the maximum dose of urokinase (25,000 IU/ml) was used, which demonstrated that 68% versus 28% of patients treated with 25,000 IU/ml urokinase or placebo, respectively, had restored CVAD function after one or two instillations[22]; however, as this was placebo-controlled, no direct comparison to alteplase can be made.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

The limited submission provided by the company does not include any evidence on the cost-effectiveness of alteplase for thrombolytic treatment of occluded CVADs, including those used for haemodialysis[20]. Cost-effectiveness evidence is not required for a limited submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

According to a survey conducted by the company, the majority of thrombolytic use for treatment of occluded CVADs is in haemodialysis patients (data on file)[20]. The company has therefore focused estimates of eligible patient populations around haemodialysis patients. Using data from the UK Renal Registry (2009)[24], the company estimates that 1,069 patients are receiving haemodialysis in Wales. Due to a lack of data on the number of patients with CVADs, the company assumes that one third of haemodialysis patients (353) have CVADs in Wales. Assuming that patients attend three haemodialysis sessions per week (156 per year), the company estimates that there are 55,000 haemodialysis sessions per year, during which CVAD occlusion could occur. It is further assumed that 20% (11,000) of these sessions may require thrombolytic treatment for occluded CVADs, of which 30% of obstructions (3,300) will be managed with alteplase each year in Wales. The management of each occlusion may require up to two doses of Actilyse® Cathflo® 2 mg. The company anticipates the cost of the new treatment will offset the cost of the currently used alteplase 10 mg, 20 mg and 50 mg. Company-reported potential costs associated with the introduction of Actilyse® Cathflo® 2 mg for thrombolytic treatment of occluded CVADs are shown in Table 1.

Table 1. Company-reported costs based on substitution of Actilyse® 10 mg, 20 mg and 50mg (assumed wastage of 0% and 50%) with Actilyse® Cathflo® 2 mg

Formulation	Cost of Actilyse® formulation	Cost of Actilyse® to produce 2 mg aliquots		Cost of Actilyse® Cathflo 2 mg	% wastage required for cost neutrality
		Assuming 0% wastage	Assuming 50% wastage		
10 mg Actilyse®	£120	£24	£48	£45	50%
20 mg Actilyse®	£180	£18	£36		60%
50 mg Actilyse®	£300	£12	£24		73%

5.1.2 WMP critique of the company's budget impact estimates

There is an apparent lack of data with which to estimate overall CVAD use and, hence, the potential use of thrombolytic treatment for occluded CVADs in Wales. No attempts have been made by the company to estimate the annual costs of thrombolytic treatment of occluded CVADs in Wales with either Actilyse® Cathflo® 2 mg or comparators. Table 1 demonstrates that Actilyse® Cathflo® 2 mg is more costly to use than Actilyse® 10 mg, 20 mg and 50 mg when the latter are used off-label to produce multiple 2 mg aliquots, whenever wastage is less than 50%, 60% or 73%, respectively. As no data are provided to determine the proportion of use of Actilyse® 10 mg, 20 mg and 50 mg to generate 2 mg aliquots for unblocking CVADs, it is not possible to determine the extent to which the costs of Actilyse® Cathflo® 2 mg will be offset by savings in the use of Actilyse® (or urokinase). It should be noted that Actilyse® has a limited shelf-life of 8 to 24 hours (depending upon storage conditions) once reconstituted[25], and so the ability to produce multiple 2 mg aliquots from the 10 mg, 20 mg and 50 mg presentations in practice is unclear, and may be associated with significant wastage. The company submission notes that that up to two Actilyse® Cathflo® 2 mg doses may be required and used to clear occluded CVADs, which may potentially double the costs of clearance with Actilyse® Cathflo® 2 mg (as with other comparators). No data are presented to explore the costs associated with this scenario, or the use of urokinase, which, according to a company-conducted survey, was the most frequently used drug for first- and second-line clearance of thrombus blockage. However, the acquisition costs of Actilyse® Cathflo® 2 mg and urokinase at a dose of up to 25,000 IU are similar (see Table 2). Combined with the uncertainty around eligible patient numbers and the proportion with CVAD occlusions, the cost analysis appears to be subject to uncertainty.

5.2 Comparative unit costs

Table 2. Examples of drug acquisition costs for licensed thrombolytic treatments for occluded CVADs

Drug	Example regimen	Cost per occluded CVAD cleared
Alteplase (Actilyse® Cathflo® 2 mg powder	2 mg/ml up to two times into dysfunctional CVAD	£45.00–90.00
Urokinase (Syner-KINASE®) 25,000 IU and 100,000 IU powder	5,000–25,000 IU/ml into dysfunctional CVAD, repeated if necessary	£45.95–91.90*
** Assuming up to two 25,000 IU vials are used[23].* *Costs are based on MIMS[26] list prices.* *This table does not imply therapeutic equivalence of drugs or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that alteplase (Actilyse® Cathflo® 2 mg) is not suitable for shared care within NHS Wales.

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