HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

23 September 2009

ACTILYSE 2 mg, powder and solvent for solution for injection
Powder in vials (glass) + 2.2 mL of solvent in ampoules (glass)
B/5 (CIP: 574 194-2)

Applicant: BOEHRINGER INGELHEIM FRANCE

Alteplase

ATC Code: B01AD02

List I - Medicinal product for hospital use only

Date of Marketing Authorisation: 03 March 2009 (mutual recognition, rapporteur country: Germany)

Reason for request: Inclusion on list of products for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Alteplase

1.2. Indication

"Thrombolytic treatment of occluded central venous access devices including those used for haemodialysis".

1.3. Dosage

"A dose of up to 2 mg alteplase administered up to two times for any one occlusion, can be used to restore function of ports, single and multiple lumen catheters including those used for haemodialysis, which became dysfunctional due to thrombotic occlusion.

Reconstitution of a final concentration of 1 mg alteplase per mL is recommended for use in this indication.

- In patients with a body weight of 30 kg or more, a total dose of 2 mg in 2 ml should be instilled into the dysfunctional central venous access device.

- In patients with a body weight below 30 kg, the volume of reconstituted solution to be instilled into the dysfunctional central venous access device should correspond to 110% of the internal lumen volume of the device. The total dose of alteplase should not exceed 2 mg. For a catheter with an internal lumen volume of 1.0 mL, the total dose of Actilyse should be 1.1 mg with a volume of 1.1 mL.

If central venous access device function is not restored at 120 minutes after the first dose, a second dose of equal amount may be instilled."

2 COMPARABLE MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

B: Blood and blood forming organs
B01: Antithrombotic agents
B01AD: Enzymes
B01AD02: Alteplase

2.2. Medicines in the same therapeutic category

Other thrombolytic agents for use in this indication:

Product	Content analysis	Indication	Posology
ACTOSOLV UROKINASE Powder for solution for injection (INN: urokinase)	100,000 IU 600,000 IU	"Restoration of permeability of venous catheters (central venous catheters and dialysis catheters) that are obstructed by a forming or recently formed thrombus".	"In case of treatment failure: if permeability is not restored, and once the position of the catheter and absence of contraindication to systemic urokinase administration are verified, an infusion can be started, as described below: - in adults, an infusion of 20,000 IU/h for haemodialysis catheters and 40,000 IU/d for other catheters for a minimum of 1 hour or until permeability is restored, with maximum dose not exceeding 250,000 IU. - in children, an infusion of 4400 IU/kg/hour according to progress on ultrasound or for a maximum of 4 hours. As a first-line treatment: the procedure can be repeated 1-4 times if necessary".
STREPTASE Powder for solution for infusion (INN: Streptokinase)	250,000 IU 750,000 IU	"Clearance of obstruction of external arteriovenous shunts in patients on haemodialysis.	5000-10,000 IU to be given over 20 minutes, to be repeated a maximum of 5 times.

2.3. Medicines with a similar therapeutic aim

None.

3 ANALYSIS OF AVAILABLE DATA

Efficacy and safety of alteplase in restoration of permeability of occluded central venous catheters in adults were evaluated in 3 studies in particular:

- two randomised trials versus placebo (study A2055g) and versus urokinase (study by Haire[1]);
- one open-label study (study A2065g).

Adult patients on dialysis with an occluded central venous catheter or synthetic arteriovenous shunt were evaluated in 12 observational studies (with or without comparator arms).

Concerning use in occluded central venous catheters in children, the following data are available:

- one open-label study (study A2404g);
- a combined analysis of data in the paediatric population (children aged under 17 in studies A2055g, A2065g and A2404g);
- four non-comparative observational studies and one case-control study.

The design and main results of the non-randomised studies are given as an annex.

3.1. Efficacy

3.1.1. Occluded central venous catheters (not dialysis)

- Versus placebo (Study A2055g)

This was a phase III randomised double-blind placebo-controlled study, in which 149 patients were included, of whom 12 were children and 7 were aged between 2 and 11 years. The objective was to evaluate the efficacy of a 2 mg dose of alteplase in removing occlusion from a central venous catheter after a contact time of 120 minutes. If needed, a second 2 mg dose of alteplase was used in patients in both arms.

The proportion of central venous catheters in which permeability[2] was restored after one dose (primary endpoint) was 73.9% (51/69) for alteplase and 17.1% (12/70) with placebo, an absolute difference of 56.8% (95% CI [41.2; 70.8], p < 0.0001).

After a second 2 mg dose of alteplase and a contact time of 120 minutes, permeability had been restored in 89.9% of the central venous catheters (62/69). The treatment was effective for all sub-groups (by type of central venous catheter, sex, age and weight).

- Versus urokinase (Study by Haire[1])

This was a phase III randomised double-blind study versus urokinase, in which 48 adult patients were included. The objective was to compare efficacy of 2 mg alteplase with 10,000 IU urokinase in clearing occluded (confirmed on X-ray) central venous catheter, after a contact time of 120 minutes. A second dose was given if needed.

The proportion of central venous catheters in which permeability[2] was restored after a maximum of two doses (primary endpoint) was 89.3% (25/28) for alteplase and 59.1% (13/22) with urokinase, an absolute difference of 30.2% (p= 0.013).

After one dose, the number of patients whose thrombus had entirely dissolved (secondary endpoint evaluated using contrast X-ray of the central venous catheter) was 46.4% in the alteplase arm and 18.2% in the urokinase arm (p = 0.036). After two doses, the proportions observed were 60.7% in the alteplase arm and 31.8% in the urokinase arm (p = 0.042).

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1 Haire WD et al**.** Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial**.** Thrombosis and Haemostasis 1994; 72(4):543-547

[2] Defined as the ability to draw 3 mL of blood and then infuse 5 mL of a normal saline solution with no resistance.

The small number of patients included limits the possibilities for generalising these results.

- Other efficacy data

In the two non-comparative safety studies (A2065g and A2404g), one to two doses of alteplase 2 mg enabled clearance of occluded central venous catheters (secondary endpoint) in 82.9%-87.2% of cases.

3.1.2 Occluded central venous catheters and synthetic arteriovenous shunts for dialysis

No randomised studies have been carried out.
The applicant has presented results of (published) observational studies that have been carried out on patients on dialysis. Restoration of permeability of central venous catheters and arteriovenous grafts used in haemodialysis has been defined in various ways, relating to increase in blood flow of the dialysis pump before and after thrombolysis of the central venous catether, presence of a thrill on palpation or auscultation, or at times using X-ray evaluation with contrast injection.

- Central venous catheters for dialysis (CVAD-D):

In seven studies [3],[4],[5],[6],[7],[8],[9] in which a total of 203 patients with dysfunctional CVAD-D were included, restoration of permeability was defined as the ability to carry out a dialysis session with a sufficient flow rate. The dialysis flow rate was improved in 70.0%-97.5% of cases, following administration of one or two doses of alteplase.
The study design and main results of these studies are given in the Annex (Table 1).

- Occluded synthetic arteriovenous grafts for dialysis (sAVG):

In four studies [10],[11],[12],[13] in which a total of 119 patients with a thrombosed sAVG were included, clearance was observed in 88-95% of cases.

An historic comparison between urokinase (250,000 IU) and alteplase (2 mg) showed that permeability restoration percentages were identical (95%). The percentage of serious complications was 2.5% for alteplase and 0% for urokinase; minor haematoma at the puncture site was reported in 20% of cases involving urokinase and 17% of cases involving alteplase.
The quality of evidence of this study is poor, given the design (observational study, methods used), which makes it difficult to interpret the results, particularly concerning effect size. The study design and main results of these studies are given in the Annex (Table 2).

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[3] Zacharias JM *et al*. Alteplase versus urokinase for occluded hemodialysis catheters. Annals of Pharmacotherapy 2003; 37(1):27-33
[4] Eyrich H *et al*. Alteplase versus urokinase in restoring blood flow in hemodialysis-catheter thrombosis. *American* Journal of Health System Pharmacy 2002; 59(15):1437-1440
[5] Savader SJ *et al*. Treatment of hemodialysis catheter-associated fibrin sheaths by rt-PA infusion: critical analysis of 124 procedures. Journal of Vascular and Interventional Radiology 2001; 12(6):711-715
[6] Spry LA, Miller G. Low-dose tPA for hemodialysis catheter clearance. Dialysis and Transplantation 2001; 30(1):10-54
[7] Daeihagh P *et al*. Efficacy of tissue plasminogen activator administration on permeability of hemodialysis access catheters. American Journal of Kidney Diseases 2000; 36(1):75-79
[8] Meers C, Toffelmire EB. Tissue plasminogen activator (t-PA) efficacy in the restoration of hemodialysis catheter function. CANNT Journal 1999; 9(4):25-28
[9] Paulsen D *et al*. Use of tissue plasminogen activator for reopening of clotted dialysis catheters. Nephron 1993; 64:468-470
[10] Cooper SG. Pulse-spray thrombolysis of thrombosed hemodialysis grafts with tissue plasminogen activator. American Journal of Roentgenology 2003; 180:1063-1066
[11] Sofocleous CT *et al*. Alteplase for hemodialysis access graft thrombolysis. Journal of Vascular and Interventional Radiology 2002; 13(8):775-783
[12] Falk A *et al*. Thrombolysis of clotted hemodialysis grafts with tissue-type plasminogen activator. Journal of Vascular and Interventional Radiology 2001; 12(3):305-311
[13] Vogel P *et al*. Thrombosed hemodialysis grafts: lyse and wait with tissue plasminogen activator or urokinase compared to mechanical thrombolysis with the arrow-trerotola percutaneous thrombolytic device. Journal of Vascular and Interventional Radiology 2001; 12(10):1157-1165

3.1.3. Efficacy data in children with CVAD

Three studies involving a total of 432 children: a sub-group of 11 children in the A2055g randomised placebo-controlled study and sub-groups in the two open-label safety studies, one with 114 children (A2065g) and the other with 307 children (A2404g). Combined analysis showed that the first dose of alteplase restored CVAD permeability in 76.6% of cases (331/432) and the 2nd dose restored permeability to 31 additional CVADs, in other words 83.8% (95% CI [80.0; 87.1]) of treated CVADs were made patent.
Although there are doubts as to the quality of the design of this analysis, the percentage of CVADs in which permeability was restored seems to be similar in children to that observed in adults.
In addition, five observational studies [14],[15],[16],[17],[18] involving a total of 381 children report restoration of permeability in between 85% and 98% of occluded catheters (see Annex, Table 3). These results tend to confirm those observed in the above analysis.

3.2. Adverse effects

The safety profile of alteplase 2 mg is based on data from clinical studies and international pharmacovigilance, as alteplase 2 mg has been marketed in North America in this indication since 2001 for adults and since 2005 for children.

Safety studies:
- Prospective non-comparative study A2065g included 997 patients, of whom 114 (12%) were children. The primary objective was to evaluate the safety of alteplase 2 mg administered in up to 2 doses and with a contact time of up to 120 minutes, in thrombolysis of occluded central venous catheters. No episodes of major or intracranial haemorrhage attributed to the treatment, and no embolic events, were reported.
- Study A2404g, a prospective non-comparative study evaluating the occurrence of adverse effects in 321 children, of whom 55 (17%) were aged under 2. After administration of alteplase 2 mg, in up to 2 doses, no intracranial or major haemorrhage and no embolic or thrombotic events were reported.

According to the SPC:
- In the available clinical studies, occurrence of septicaemia and catheter-related complications are "uncommon", and fever is "rare".
- Alteplase has not been studied in patients at particular risk of haemorrhage when administered with a thrombolytic agent (active internal bleeding, recent surgery, thrombocytopenia and other coagulation disorders linked to renal or hepatic impairment). "In addition, formation of antibodies in patients receiving one or more doses of alteplase has not been studied".
- In the treatment of occluded, if alteplase passes into the general circulation, all the adverse effects that have been observed for other indications (systemic administration) can occur. However, this risk appears to be very limited.

International pharmacovigilance data since 2001 confirms that there is a low incidence of adverse effects involving alteplase 2 mg in this indication, in both adults and children:
- Between September 2001 and September 2005, 42 adverse effects were reported, among 1.6 million patients exposed to alteplase 2 mg. Half were in the category "general disorders and administration site conditions", including 14 cases of lack of efficacy, 3 non-fatal thromboembolisms, 3 haemorrhages at catheter insertion site.

[14] Chesler L, Feusner JH. Use of tissue plasminogen activator (rt-PA) in young children with cancer and dysfunctional central venous catheters. Journal of Pediatric Hematology/Oncology 2002; 24(8):653-656
[15] Iqbal Y *et al*. Cryopreserved recombinant tissue plasminogen activator for the restoration of occluded central venous access devices in pediatric oncology patients. Annals of Saudi Medicine 2002; 22(5/6):300-302
[16] Choi M *et al*. The use of alteplase to restore permeability of central venous lines in pediatric patients: a cohort study. Journal of Pediatrics 2001; 139(1):152-156
[17] Bussières JF *et al*. Efficacy of urokinase and alteplase to reopen occluded central venous catheters in children. Journal of the Pharmacy Technology 2001; 17(3):95-98
[18] Jacobs BR *et al*. Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. Journal of Pediatrics 2001; 139(4):593-596

- Between September 2005 and September 2008, 52 adverse effects were reported, of which 13 were serious. The most commonly reported were lack of efficacy (incomplete thrombolysis of catheter: 65.4%, catheter-linked complications: 11.1%).

3.3. Conclusion

Alteplase (ACTILYSE) in its 10 mg presentation was previously used off-label for restoration of permeability of central venous catheters in France. A 2 mg dose is now indicated in adults and children for "thrombolysis of occluded central venous catheters, including those used in haemodialysis".

For treatment of CVADs, efficacy results are:

- In one randomised study, a 2 mg dose of alteplase restored permeability in 73.9% of cases versus 17.1% with placebo, giving an absolute difference of 56.8%; if the first dose failed, the second dose restored permeability in 83-90% of cases.
- In one randomised study[1], the proportion of central venous catheters in which permeability was restored (primary endpoint) after a maximum of two doses was 89.3% (25/28) for alteplase (2 mg/dose) and 59.1% (13/22) for urokinase (10,000 IU/dose), an absolute difference of 30.2% with alteplase being superior (p= 0.013). The extent to which these results can be generalised is arguable, however, because of the small numbers involved (50 catheters).

In patients on haemodialysis with a dialysis CVAD (n = 539) or a synthetic arteriovenous graft (sAVG, n = 119), results of 11 observational studies including a total of 322 patients have shown rates of restoration of permeability of between 88 and 95% for sAVGs and between 70 and 97.5% for CVAD for dialysis. These results suggest that efficacy is similar to that observed for CVADs.

Overall, the data for adults suggest that alteplase provides restoration of CVADs and dialysis CVADs at a similar or slightly better rate to urokinase in adults.

In children, the data from 3 studies involving 432 children suggest that efficacy is similar to that observed in adults. Clinical data available for children under 2 are very limited.
The incidence of adverse events was low. The majority of these were catheter-related complications (infection, septicaemia, administration site conditions).
The Committee notes that the dose (2 mg) and packaging (powder in a glass vial and 2.2 mL solvent in a glass ampoule) are appropriate for this indication, for both adults and children. Administration of ACTILYSE 2 mg is done according to a written administration protocol, which ensures simple and safe use.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The use of intravenous catheters is required in various clinical situations: chemotherapy, parenteral nutrition, antibiotic therapy, transplant, intensive care, resuscitation, and for access for dialysis in the absence of arteriovenous fistula.

These venous access devices, which are inserted for the long term into deep veins, either as simple or tunnelled catheters or as port-a-caths, can cause mechanical, thrombotic or infectious complications. The presence of a thrombus in the lumen of the catheter leads to reduction or complete obstruction of the blood flow, requiring either conservative intervention (thrombolysis) or catheter replacement.

Removal of a thrombosed catheter and insertion of a new one carries risks of morbidity and mortality. In addition, in children, sedation followed in most cases by general anaesthesia are required in order to insert a new catheter in safety and comfort, and these measures carry their own risks.

Public Health Benefit

The public health burden represented by complications linked to occlusion of central venous catheter is difficult to quantify.

By restoring permeability of occluded central venous catheters, thus avoiding the need for removal of catheter and insertion of a new one, ACTILYSE has a moderate impact on morbidity linked to manipulation of central venous catheters (pneumothorax, haematoma or haemorrhage) and on the associated reduction in quality of life. This is particularly important for children, for whom this procedure is painful, poorly tolerated, and requires surgical intervention, often involving general anaesthesia. Prevention of pain, particularly in the therapeutic management of children, is defined as a priority. However, given the inadequate quality of data demonstrating efficacy, and given the existing therapeutic alternatives, the additional impact of ACTILYSE is weak at best. ACTILYSE provides a partial response to the public health need that is already partially met by the other available fibrinolytics.

ACTILYSE has no impact on the way in which the healthcare system is organised.

As a result, ACTILYSE is not expected to benefit public health. This benefit is low.

The efficacy/adverse effects ratio for alteplase is high.

ACTILYSE 2 mg is a first-line therapy. Alternative medicinal products exist: urokinase, or streptokinase in exceptional cases.

The actual benefit of ACTILYSE 2 mg is substantial.

4.2. Improvement in actual clinical benefit

ACTILYSE 2 mg provides a minor improvement in actual benefit (IAB IV) in terms of efficacy in comparison with ACTOSOLV UROKINASE.

4.3. Therapeutic use

Comfort and safety of repeated administration of parenteral drugs, and of multiple sessions of dialysis, often require the insertion of long-term venous access into a deep vein, either in the form of a central line or a port-a-cath.

These catheters can become thrombosed. There are two therapeutic options for restoring permeability: use of a thrombolytic agent or insertion of a new catheter.

Thrombolytic agents are injected into the lumen of the occluded catheter, and two drugs have marketing authorisation for this indication: urokinase and, now, alteplase.

The packaging of ACTILYSE 2 mg is better suited to this indication than that of ACTOSOLV UROKINASE.

4.4. Target Population

The target population of patients requiring prescription of ACTILYSE corresponds to the set of patients with venous catheters (central or for dialysis):

- patients on haemodialysis (catheters and arteriovenous grafts);
- patients with central venous catheters for chemotherapy, parenteral nutrition, antibiotic therapy, transplants, intensive care, in resuscitation or with port-a-caths;

those who require fibrinolytic treatment to restore permeability of a catheter that is occluded by forming or recently formed thrombus.

Estimation of the target population

Around 150,000 port-a-caths and 40,000 long-term catheters are inserted each year in France. Occlusion seems to occur in 3-5% of cases, at least once per year (expert opinion), giving 5700-9500 episodes of occlusion.

According to National Health Insurance and INSEE data:
- the prevalence of terminal renal failure requiring dialysis in France in 2003 was 513 per million inhabitants[19]
- The French population in 2008 was 63.8 million[20] and 32729 patients underwent haemodialysis in 2008;
- Almost 66% of these patients undergoing dialysis have a CVAD-D or a sAVG and one third of these devices have dysfunction that is linked to thrombosis [Little, Walshe 2002; Raaf 1985], meaning that 7200 patients are affected.

In total, given these figures, at least 12900-16700 patients are affected by thrombotic occlusion of their CVAD.

4.5. Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the extension of indication "restoration of permeability of venous catheters (central venous catheters and dialysis catheters) with obstruction linked to forming or recently formed thrombus" and at the dosage of the marketing authorisation.

The Committee notes that the packaging of ACTILYSE 2 mg is better suited to this indication than that of ACTOSOLV UROKINASE.

[19] CNAM, 2004
[20] Eurostat, 2008

Table 1: Evaluation of efficacy and safety of alteplase in clearing occluded central venous catheters in haemodialysis							
Study	**Design**	**Patients treated**	**Treatment arms**	**Duration of treatment**	**Inclusion criteria**	**Efficacy**	**Safety**
[Zacharias *et al*. 2003]	Observational study Historical comparison with urokinase	30	Filling lumen of catheter Alteplase 1 mg/mL: n=30 Urokinase 5000 IU/mL: n=14	Contact time 30 minutes	Age > 18 years Q_b < 200 mL/min	Restoration of Q_{sg} ≥ 200 mL/min for completely occluded central venous catheters Alteplase: 88.2% (15/17) Urokinase: 42.9% (6/14) Difference: 45.3%; p = 0.018	No adverse events
[Eyrich *et al*. 2002]	Observational study	37	Alteplase 1 mg: n=27 Urokinase 5000 IU: n = 10	Contact time 60 minutes	Q_{sg} ≤ 300 mL/min	Q_{sg} > 300 mL/min for 30 minutes Alteplase: 70% Urokinase: 35% p = 0.013	No haemorrhage
[Savader *et al*. 2001]	Observational study	55 (124 catheters)	Alteplase 2.5 mg/50 mL infused via catheter	Infusion over 3 hours	Q_{sg} < 300 mL/min	Q_{sg} > 300 mL/min: 91.1% (113/124)	No adverse events
[Spry, Miller 2001]	Observational study	44	Alteplase 2.5 mg Maximum dose 5 mg	Over maximum 1 hour	Q_b < 100 mL/min or Venous line pressure > 250 mmHg with Q_b < 200 mL/min	Haemodialysis session carried out successfully in 81%-97% of cases Qb > 300 mL/min in 44-59% of cases, depending on location of CVAD-D	No adverse events
[Daeihagh *et al*. 2000]	Observational study	22 (28 catheters)	Alteplase: 4 mg (2 mg per catheter lumen)	2-96 hours	Q_b < 200 mL/min	Q_b ≥ 200 mL/min: 87.5% (49/56)	No adverse events
[Meers, Toffelmire 1999]	Observational study	17 (21 catheters)	Filling lumen of catheter Alteplase: 1 mg	40 minutes	Q_b insufficient	Improvement of Q_b 97.5% (39/40)	No adverse events

[Paulsen *et al*. 1993]	Observational study	8 (18 catheters)	Filling lumen of catheter Alteplase: 2 mg	30 min - 4 days	Q_b < 150 mL/min	Q_b < 200 mL/min 83.3% (15/18)	No adverse events

CVAD-D: Central venous access device for dialysis; Q_b = blood flow (dialysis pump)

Table 2: Evaluation of efficacy and safety of alteplase in restoration of permeability of sAVG occluded by thrombus in patients on dialysis

Study	Methodology	Patients treated	Treatment arms	Duration of treatment	Inclusion criteria	Efficacy	Safety
[Cooper 2003]	Observational study	17	Pulse Spray Total alteplase dose 2 mg	16 minutes	Thrombosed sAVG	Restoration of permeability of sAVG 94.1% (16/17) Proportion maintaining permeability of sAVG at 1 month: 71%; at 3 months: 47%	No haemorrhage
[Sofocleous *et al*. 2002]	Observational study	49 (68 sAVG)	Pulse Spray Mean dose of alteplase 4.5 mg (n = 41) L&W Mean dose of alteplase 3.7 mg (n = 27)	Pulse Spray mean duration 78 minutes L&W mean duration 69 minutes	Thrombosed sAVG	Restoration of permeability of sAVG 94.1% (64/68) Pulse Spray: 95.1% (39/41) L&W: 92.6% (25/27) Proportion maintaining permeability of sAVG at 1 month: 72%; at 3 months: 57%	2 episodes of major bleeding (duration > 30 minutes) at the puncture site 2 arterial emboli
[Falk et al 2001]	Observational study	33 (42 sAVG)	Alteplase 2 mg with heparin 3000-5000 IU Volume injected 5 mL	Mean 41 minutes	Thrombosed sAVG	Restoration of permeability of SAVG 88.1% (37/42) Proportion maintaining permeability of SAVG at 1 month: 57%; at 3 months: 50%	No major haemorrhage

[Vogel et al 2001]	Historic comparison 2 parallel groups L&W alteplase Percutaneous thrombectomy + historic group L&W urokinase	60	L&W alteplase 4 mg (n = 20) Percutaneous thrombectomy (n = 20) L&W urokinase 250,000 IU (n = 20)	L&W alteplase 10.5 minutes Percutaneous thrombectomy 19 minutes L&W urokinase 14 minutes	SAVG inserted more than 2 weeks previously and with thrombosis for past < 2 weeks	Restoration of permeability of SAVG 95.0% (19/20), in all treatment arms Proportion maintaining permeability of SAVG at 3 months: L&W alteplase: 65% Thrombectomy: 65% L&W urokinase: 60%	L&W alteplase 4 mg: 6 cases of bleeding at puncture site Percutaneous thrombectomy: 1 case of arterial embolism L&W urokinase: 4 cases of bleeding at puncture site

SAVG: Synthetic arteriovenous graft; L&W: Lyse and Wait

Table 3: **Paediatric population: Evaluation of efficacy and safety in published clinical studies**							
Study	Methodology	Children treated	Treatment arms	Duration of treatment	Inclusion criteria	Efficacy	Safety
[Chesler, Feusner 2002]	Observational study	42	Alteplase: 0.5 mg	Up to 2 doses Contact time 30-60 minutes	Children with cancer, weighing < 30 kg and with an occluded CVAD	Restoration of permeability of central venous catheter: 88.1% (37/42) Proportion with repeat occlusion at 1 month: 37.8% (14/37)	1 bleeding 3 reduced haemoglobin
[Iqbal et al 2002]	Observational study	40	Alteplase: Weight ≤ 10 kg: 0.5 mg Weight > 10 kg: 1 mg max	One dose Contact time 60-120 minutes	Age < 13 years Acquired occlusion of CVAD	Restoration of permeability of CVAD: 97.5% (39/40)	No adverse events
[Bussière *et al*. 2001]	Case (alteplase)-control study (urokinase) 1 case per 2 controls	133	Alteplase: n=46 Mean dose: 1.22 mg Urokinase: n = 87 Mean dose: 4830 IU	Mean contact time Alteplase: 206 minutes Urokinase: 207 minutes	Children with CVAD with thrombolytic treatment with alteplase (case) or urokinase (controls)	Restoration of permeability of central venous catheter: Alteplase: 93.2% Urokinase: 54.5% OR = 11.4 (95 % CI [3.2; 40], p <0.001).	No haemorrhage
[Choi et al 2001]	Observational study	25 (34 CVADs)	Alteplase: Weight ≤ 10 kg: 0.5 mg Weight > 10 kg: 2 mg maximum	One dose Contact time 120-240 minutes	Children with occluded CVAD	Restoration of permeability of CVAD: 85.3% (29/34)	1 neck haematoma 1 distal deep vein thrombosis
[Jacobs *et al*. 2001]	Observational study	228 (320 CVADs)	Alteplase: 110% of internal volume of CVAD 2 mg maximum	Up to 3 doses Contact time 20 minutes	Children with occluded catheter	Restoration of permeability of CVAD: After 1 dose: 71.3% (228/320) After 2 doses: 86.8% After 3 doses: 90.6%	No adverse events