TRANSPARENCY COMMITTEE

OPINION

14 February 2007

ACTOSOLV UROKINASE 100,000 IU, powder for solution for Injection
6-ml glass bottle (CIP: 565 106-7)

ACTOSOLV UROKINASE 600,000 IU, powder for solution for Injection
25-ml glass bottle (CIP: 565 107-3)

Applicant: EUMEDICA

Urokinase

ATC code: B01AD04

List I

Date of Marketing Authorisation (national registration procedure): June 19, 1985
MA variation March 31, 2006 (extension of indication)

Reason for request: Change in the conditions of inclusion.
Inclusion on the list of medicines approved for use by hospitals in the extension of indication
“Restoration of patency of intravascular catheters (central venous catheters and
dialysis catheters), blocked by a forming or recently formed thrombus”.

Medical, Economic and Public Health Assessment Division
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Urokinase

1.2. Indications
- Restoration of patency of intravascular catheters (central venous catheters and dialysis catheters), blocked by a forming or recently formed thrombus (extension of indication).

- Treatment of arterial and venous occlusions caused by a forming or recently formed thrombus, of pulmonary emboli, in particular when a recent thrombolytic treatment by streptokinase contraindicates its use.

1.3. Dosage
In restoring venous catheter patency (central venous catheters and catheters of dialysis):

First-line:
- Check that the catheter is blocked by trying to draw blood using a syringe.

If this fails, draw in and then inject urokinase according to the recommended dosage:
- In adults: inject a solution at a concentration of 5,000 to 10,000 IU/ml, depending on the volume of the catheter. This must be injected into each blocked branch.
- In children: inject a solution at a concentration of 5,000 to 10,000 IU/ml, depending on the volume of the catheter or 4,400 IU/kg. This must be injected into each blocked branch.

- After waiting at least 15 to 30 minutes, try to draw blood through the catheter.
- Check the restoration of patency after at least 15 to 30 minutes.
- This procedure may be repeated 1 to 4 times if necessary.

In the case of failure
If patency is not restored, after checking the position of the catheter and provided there is no contraindication to the systemic administration of urokinase, an infusion may be performed as described below.
- Infusion in adults of 20,000 IU/h for haemodialysis catheters and 40,000 IU/h for the other catheters over a period of no less than one hour or until flow is restored without exceeding a maximum dose of 250,000 IU.
- Infusion in children of 4,400 IU/kg/h with ultrasound monitoring or for at least 4 hours.
2.1. ATC 2005 classification

B : BLOOD AND HAEMATOPOIETIC ORGANS
B01 : ANTITHROMBOTIC AGENTS
B01AD : ENZYMES
B01AD04 : UROKINASE

2.2. Medicines in the same therapeutic category

Comparator medicines

In the extension of indication: “Restoration of patency of venous catheters (central venous catheters and dialysis catheters) blocked by a forming or recently formed fibrin clot”: None

Thrombolytic medicinal products that may be used “off-label” in this indication:

<table>
<thead>
<tr>
<th></th>
<th>Proprietary product</th>
<th>Pharmaceutical form Route of administration</th>
<th>Packaging</th>
<th>Marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>alteplase</td>
<td>ACTILYSE</td>
<td>Powder and solvent for solution for IV injection and infusion</td>
<td>Vial of 10, 20, 50 mg</td>
<td>Approved for hospitals.</td>
</tr>
<tr>
<td>streptokinase</td>
<td>STREPTASE</td>
<td>Powder for solution for Injection containing 250,000, 750,000, 1,500,000 IU</td>
<td>Powder vial</td>
<td>Approved for hospitals.</td>
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2.3. Medicines with a similar therapeutic aim

None

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1 Urokinase promotes the transformation of plasminogen into plasmin (fibrinolytic of human origin).
According to the Public Evaluation Report by AFSSAPS of April 2006, “A wide review of the literature shows that the use of urokinase already forms part of the established medical practice as shown by more than 10 years of publications and that it has a real efficacy in restoring the patency of occluded central venous catheters and dialysis catheters; urokinase was effective in nearly 80 to 90% of cases with few haemorrhagic accidents; its use appears to be safe. Its efficacy and safety have been evaluated in non-comparative studies and in comparative studies versus placebo and other thrombolytic agents”.

3.1. Efficacy
The studies submitted include the results of the following studies:

1- A recent dose-ranging study

2- Studies evaluating the efficacy and safety of urokinase for unblocking haemodialysis catheters and in particular:
- A systematic review of studies of urokinase, streptokinase and alteplase: urokinase concentrations initially used as bolus doses ranged from 5,000 to 9,000 UI/ml in each lumen and as an infusion of 125,000 IU per lumen (250,000 IU for 2 lumens). Observed patency restoration rates were from 70 to 80% with urokinase and 44 to 98% with alteplase; a single episode of minor bleeding was reported with urokinase and up to 17% with alteplase.

- A meta-analysis of 13 comparative studies on 3,287 patients (1,850 treated with urokinase and 1,437 with alteplase) gave patency restoration rates of 97% with urokinase and 81% with alteplase. Mean urokinase concentrations used were 5,460 ± 7,660 IU. No major bleeding was observed with urokinase compared to 0.22% of major bleeding with alteplase.

- The results of an historical comparison between urokinase (250,000 IU) and tissue plasminogen activator (TPA) (4mg) in the treatment of thromboses of prosthetic arteriovenous fistulas for haemodialysis gave an identical percentage of restoration of patency of 95%; a percentage of serious complications of 2.5% for TPA and 0% for urokinase; minor hematomas at the puncture site in 20% of cases with urokinase and 17% of cases with TPA.
  Ref.: P.M. Vogel 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. J Vasc Interv Radiol 2004;15: 575-579.
3- Studies evaluating the efficacy and safety of urokinase for unblocking other central venous catheters and in particular:

- A randomised double-blind study versus placebo (Haire, 1994) showed the value of the administration of urokinase (5,000 IU/ml) in 50 cases of catheter thrombosis (48 patients) compared to t-PA (2 mg). Injections of urokinase could be repeated in the case of non-functional restoration and when necessary by infusion of 40,000 IU/h over 6 hours. Only three catheters did not recover complete patency. No complication was noted.

- In 1999, Whigham retrospectively evaluated the effect of urokinase in 391 patients with central venous catheters who had a total of 137 occlusions treated by urokinase injections at a concentration of 5,000 IU/ml. If restoration of patency was not obtained within 15 minutes, a 2nd or even a 3rd injection was made at the same concentration (maximum total of 15,000 IU/ml). If patency was not restored within 15 minutes after the final injection, an instillation of 40,000 IU per lumen was given. This protocol restored patency in 99% of cases. No treatment-related complication was observed. Ref.: C.J. Whigham et al. Incidence and management of catheter occlusion in implantable arm ports: results in 391 patients. JVIR 1999;10:767-774.

4- Studies evaluating urokinase in this indication specifically in children:

- A randomized study compared urokinase (solutions of 5,000 IU/ml) with placebo after injection of a sufficient volume to fill the blocked lumens. Instillations were repeated where necessary. After treatment with up to 2 instillations, urokinase restored catheter patency in 54% of the 180 patients and was more effective than placebo (30%), p = 0.002. The percentage restoration of patency was 69% in infants (adults represented nearly 80% of the study sample). No serious haemorrhagic complication was observed but minor bleeding was reported in 5% of the urokinase group. Ref.: W.D. Haire et al. Recombinant urokinase for restoration of patency in occluded central venous access devices. Thromb Haemost. 2004;92(3):575-82.

- In a study conducted in children hospitalised in intensive care, 26 cases of thrombosed central venous catheters were treated by bolus doses of 4,400 IU/kg urokinase for 10 min, followed by an infusion of 4,400 IU/kg/h. The infusion was continued either until complete thrombolysis or, in the case of a partial response, until stabilisation of the thrombus on the ultrasound scan, for 2 to 3 days. Thrombolysis was complete in 50% of the children, partial in 12% and absent in 38%. Two children had a minor haemorrhagic complications; no other adverse event was reported. Ref.: Wever ML, Liem KD, Geven WB, Tanke RB. Urokinase therapy in neonates with catheter related central venous thrombosis. Thromb Haemost. 1995 ;73(2):180-5.

- A study was conducted in 227 children managed in haematology/oncology departments. The objective of the study was to evaluate the efficacy of a continuous infusion of 200 IU/kg/day of urokinase for restoring catheter patency, after the failure of 2 bolus doses of urokinase. Functionality was not restored in 14 out of 58 blocked catheters occurring over a 1-year period (for 254 catheters), after 2 doses of urokinase. An analysis showed that catheter functionality was obtained in 11 out of 12 children treated by 200 IU/kg/h of urokinase. No coagulation disorder or sign of haemorrhage was associated with urokinase administration. Ref.: Bagnall HA, Gomperts E, Atkinson JB. Continuous infusion of low-dose urokinase in the treatment of central venous catheter thrombosis in infants and children. Pediatrics. 1989;83(6):963-6.
The following results were obtained for 21 occluded catheters (14 children aged from 2 months to 19 years) and treated by the administration of 2,500 IU/ml of urokinase in each catheter lumen: 12 immediate restorations of flow, 2 catheters that remained partially blocked, 4 catheters which had to be removed and 3 broken catheters.


3.2. Adverse effects

The risk of haemorrhagic complications is very low at the dosages recommended in the MA.

3.3. Conclusion

The extension of the indication of urokinase in adults and children to “Restoration of patency of intravascular catheters (central venous catheters and dialysis catheters), blocked by forming or recently formed fibrin clots” is based on a review of the literature confirming established medical practice, in particular in haemodialysis.

This extension of indication officialises a practice recommended by certain learned societies, in particular within the scope of haemodialysis.

Clinical data suggest that urokinase gives a similar patency restoration rate to alteplase for catheters for haemodialysis and intermediate or long-term access (central catheters); alteplase does not have this indication in its French MA.

According to the experts, few data are available for catheters used for very short-term access (less than 15 days) in children.
In the extension of indication “restoration of patency of intravascular catheters (central venous catheters and dialysis catheters), blocked by forming or recently formed fibrin clots”.

4.1. Actual benefit

Intravenous catheters are used in numerous clinical conditions: Central venous catheters are used for chemotherapy, parenteral nutrition, antibiotic therapy, transplantation, intensive care, critical care but also in nephrology for vascular venous for haemodialysis apart from arteriovenous fistulas.

The implantation of a long-term venous access device in a deep vein either as a catheter or an implantable chamber may cause mechanical, thrombotic or infectious complications. The presence of a thrombus in the catheter lumen(s) causes a reduction or blockage of blood flow requiring either conservative therapy (thrombolysis) or the replacement of the catheter.

It is particularly desirable not to have to withdraw a thrombosed catheter and implant a new catheter both in adults and in children. In paediatrics in particular, this painful surgical procedure requires general anaesthesia.

Public Health Benefit
The public health burden due to complications caused by thrombosed venous catheters is difficult to quantify.

Urokinase, which has clearly been shown to restore patency in intermediate or long-term haemodialysis catheters, has an impact on the reduction in morbidity caused by thrombus formation in venous catheters.

Urokinase may be used in particular to avoid placing a new catheter, and consequently reduces the morbidity (pneumothorax, haematoma or haemorrhage) and reduction in quality of life associated with this intervention. This is particularly important in children in whom this intervention if painful, poorly accepted, and often requires surgery performed under general anaesthesia.

For this reason, ACTOSOLV benefits healthcare organization and partially answers a public health need which is to prevent pain, in particular during the therapeutic management of children (GTNDO priority).

Consequently, ACTOSOLV benefits Public Health. This benefit may be quantified as small.

ACTOSOLV UROKINASE is a product for first-line use.
The efficacy/safety ratio is high. There are alternative products (for off-label use in this indication): alteplase, or even streptokinase.

The actual benefit of ACTOSOLV UROKINASE is substantial.
4.2. Improvement in actual benefit
In the indication “restoration of patency of intravascular catheters (central venous catheters and dialysis catheters), blocked by forming or recently formed fibrin clots” the proprietary products ACTOSOLV UROKINASE 100,000 and 600,000 IU provides a moderate improvement in actual benefit (IAB III) during their therapeutic use.

4.3. Therapeutic use
Comfortable and safe administration of drugs by the parenteral route and repeated haemodialysis often require the implantation of long-term venous access devices in a deep vein either in the form of catheters or implantable chambers. Intravenous catheters are used for treatment in numerous clinical settings: chemotherapy, parenteral nutrition, antibiotic therapy, transplantation, intensive care, resuscitation and also in nephrology for vascular access for haemodialysis, in addition to arteriovenous fistulas. These devices may cause mechanical, thrombotic or infectious complications.

There are two alternative ways for dealing with blocked catheters: use of a thrombolytic agent or surgical removal. It is particularly desirable in infants and children to avoid having to withdraw a thrombosed catheter and implant a new catheter as these operations require surgery under general anaesthesia and may give rise to complications.

The use of urokinase to restore the patency of central venous catheters and dialysis catheters blocked by a forming or recently formed fibrin clot has been recognized for many years. In the United States, urokinase is marketed with the name Open Abbokinase Cath for the restoration of flow though intravenous catheters, including central venous catheters, blocked by clots of blood or fibrin. In France, ACTOSOLV UROKINASE 100,000 and 600,000 IU has also used in this indication for many years by clinicians. It now has an indication validated by the MA Committee. This extension of indication therefore officialises a practice which has been recommended by certain learned societies (AFSSAPS Public Evaluation Report/April 2006).

In addition, in comparison with other thrombolytic medicinal products (used in this indication without an indication validated by the MA committee), streptokinase has been found to be associated with a high allergic risk, especially after repeated use (contraindicating its re-use in patients exposed to recurrences).

4.4. Target population
The target population of patients concerned by the prescription of ACTOSOLV UROKINASE in this extension of indication comprises (qualitative definition):
- Patients with a venous catheter (central or dialysis)
  - Haemodialysed patients (catheters and arteriovenous fistulas)
  - Patients with central venous catheters for chemotherapy, parenteral nutrition, antibiotic therapy, transplantation, intensive care, resuscitation or with implantable chambers
- and requiring treatment by a fibrinolytic to restore the patency of a catheter blocked by a forming or recently formed thrombus.

No reliable numerical estimation of this target population may be proposed.
4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion of the medicinal product ACTOSOLV UROKINASE 100,000 and 600,000 IU powder for solution for injection on the list of medicines approved for use by hospitals and various public services in the extension of indication “restoration of patency of intravascular catheters (central venous catheters and dialysis catheters), blocked by a forming or recently formed thrombus” and at the posology of the Marketing Authorisation.

The Committee requires the development of packaging more appropriate for use in children.