The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

SUMMARY INFORMATION ON A REFERRAL OPINION FOLLOWING AN ARBITRATION

PURSUANT TO ARTICLE 29 OF DIRECTIVE 2001/83/EC, FOR

ACTILYSE

International Non-Proprietary Name (INN): Alteplase

BACKGROUND INFORMATION

On 30 September 2002, the European Commission issued a Decision valid throughout the European Union for the medicinal product Actilyse, which contains alteplase. This decision was based on the arbitration assessment report and on the favourable opinion adopted by the Committee for Proprietary Medicinal Products (CPMP) on 27 June 2002. The Marketing Authorisation Holder responsible for this medicinal product is Boehringer Ingelheim Pharma KG.

The new approved indication subject of arbitration is "for fibrinolytic treatment of acute ischemic stroke".

Between 12 September and 14 September 2000 Boehringer Ingelheim Pharma KG, submitted applications for Mutual Recognition of the Marketing Authorisation granted on 21 August 1999 by the German Competent Authorities, acting as Reference Member State, for Actilyse, *powder and solvent for solution for injection and infusion*. The Mutual Recognition procedure started on 23 September 2000. The Concerned Member States were Austria, Belgium, Denmark, Greece, Spain, Finland, Ireland, Italy, Luxemburg, France, the Netherlands, Portugal, Sweden and the United Kingdom.

The Concerned Member States; the Netherlands, Spain, Greece and the United Kingdom, not being able to agree with the Mutual Recognition of the Marketing Authorisation granted by the Reference Member State referred the reasons for disagreement to the EMEA on 22 December 2000.

The main points to be considered by the CPMP were:

- Whether there is sufficient clinical data with reference to efficacy as well as safety e.g. risk of intra-cranial bleeding, to grant a Marketing Authorisation for the new indication *'For fibrinolytic treatment of acute ischaemic stroke'* without putting public health at risk. In particular, the major concern for most of the Concerned Member States was the lack of replication of the favourable results of the pivotal US trial (Study NINDS B) in the European studies (ECASS-I and ECASS-II) as well as in another US trial (Atlantis);
- The need to introduce further requirements in the SPC to ensure a safe use of the product.

The Reference Member State sent its report to the EMEA on 10 January 2001. The matter was referred to the CPMP on 25 January 2001. The Marketing Authorisation Holder provided supplementary information on 9 August 2001. Written explanations were provided by the Marketing Authorisation Holder on 22 March 2002 and on 29 May 2002. Additional written explanations were provided on 20

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June 2002. The Marketing Authorisation Holder provided oral explanations at a hearing before a CPMP Ad Hoc expert group on 22 April 2002 and at hearings before the CPMP plenary on 20 February 2002 and 23 April 2002.

An overall summary of the scientific evaluation is provided, together with the amended Summary of Product Characteristics (SPC) of the Reference Member State (see Annex I).

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ACTILYSE

Introduction:

Actilyse is supplied as a powder and solvent for solution for injection and infusion.

The active substance of Actilyse is alteplase. Alteplase (t-PA) is a recombinant human tissue-type plasminogen activator (t-PA). It is produced by expression of the human gene for t-PA in CHO cells. Alteplase is glycosylated. The mechanism of action is thought to be the alteplase-induced enzymatic cleavage of plasminogen into plasmin, with subsequent further increase in fibrinolysis.
Alteplase has specificity for fibrin and is considerably more active when bound to the surface of fibrin. Alteplase is distributed largely to the vascular space and is rapidly cleared from plasma. The plasma half-life is 4-5 minutes. For the residual part remaining in deep compartments, the half-life is 40 minutes.

Alteplase is previously indicated for thrombolytic treatment of acute myocardial infarction (AMI) and of acute massive pulmonary embolism (APE).

In acute myocardial infarction (AMI), a 2-dose-regimen is recommended:
The 3-hour infusion regimen, a total of 100 mg is administered (10 mg bolus, 50 mg infusion over 60 minutes and 10 mg infusion over 30 minutes, repeated until the 100 mg dose is reached). In patients weighing < 65 kg, the maximum dose is 1.25 mg/kg.
The accelerated dose regimen, a total of 100 mg is administered (15 mg as bolus, 50 mg infusion over 30 minutes and 35 mg infusion over 60 minutes).

In acute pulmonary embolism (APE), the recommended total dose is also 100 mg (10 mg bolus and 90 mg infusion over 2 hours), the total dose should not exceed 1.5 mg/kg in patients weighing < 65 kg.

The approved indication at day 90 of the Mutual Recognition procedure, before the arbitration, was: *'For fibrinolytic treatment of acute ischaemic stroke'.*
The recommended dosage for treatment of acute ischaemic stroke is 0.9 mg/kg (10% bolus and 90% as one-hour infusion), with a maximum 90 mg dose.
Alteplase is registered for treatment of acute ischaemic stroke in the US (1996), Canada (1999), and Germany (2000).

Basis for arbitration procedure*:*

Questions were raised by the Netherlands, Spain, Greece and the UK.

The basis for the arbitration procedure was:

- The need to establish whether there are sufficient clinical data with reference to efficacy as well as safety to grant a Marketing Authorisation for the new indication *'For fibrinolytic treatment of acute ischaemic stroke'* without putting public health at risk. In particular, the major concern for most of the Concerned Member States was the lack of replication of the favourable results of the

pivotal US trial (Study NINDS B) in the European studies (ECASS-I and ECASS-II), as well as in another US trial (Atlantis). Concerns were raised that the data in support of the dose and time window proposed are insufficient for reassurance that the risk-benefit assessment is positive. The benefit appears modest and there was concern regarding the frequency of intracranial haemorrhage (ICH). Moreover, the modest observed benefits are only apparent if the product is used less than 3 hours after the onset of symptoms. There is concern about the risk-benefit, which is markedly reduced outside this time frame. The basis for selecting the optimal dose should be better defined and the rational for the selected dose further justified.

- The need to introduce further requirements in the Summary of Product Characteristics (SPC) to ensure a safe use of the product.

Scientific concerns identified during the assessment procedure:

A number of public health concerns were initially identified by the CPMP during the evaluation procedure. The evidence was considered insufficient that alteplase used in acute stroke is efficacious and safe in the European setting. In one phase III study (NINDS part B) an unequivocal positive result was shown. However, this positive result was not confirmed, for the 0-3 hours subgroup, in the European stroke (ECASS I/II) studies. The Applicant was asked to justify the extrapolation from the American study to the European population and to discuss the overall benefit/risk ratio of Actilyse in the patient population expected to be treated in the EU. Further, the basis for selecting the optimal dose was not well defined and the minimal effective dose was not known. The Committee considered the benefits modest and only apparent if the product is used less than 3 hours after the onset of symptoms. The risk-benefit was considered markedly reduced outside this time frame due to the frequency of intracranial haemorrage. Furthermore, methodological concerns were identified with reference to the meta-analysis conducted by the Applicant and it was considered not to resolve the inconsistent results observed in the pivotal studies in full. The CPMP considered that the overall estimate in the meta-analysis was driven to a large extent by the positive results of the NINDS studies, of which NINDS A was considered a pilot study triggering the NINDS B. At the early stages of the procedure, the CPMP therefore expressed concerns on whether the data are sufficient at the dose and time window proposed for reassurance that the risk-benefit assessment is positive. In view of the written responses provided by the Applicant, the Committee concluded that there was a need for an Ad Hoc Expert meeting.

Recommendations from the CPMP Ad hoc Expert meeting:

The Marketing Authorisation Holder discussed the need for confirmatory data in the European setting and how to address the commitment to perform a placebo controlled confirmatory study in the time window of 3-4 hours (2x300 patients) at a hearing before the Ad hoc Expert group on 22 April 2002.

The nominated national experts who participated in the Ad hoc Expert meeting emphasised that alteplase is a widely accepted therapy among neurologists within the EU today. The experts were of the view that the results from the US trials may to some extent be extrapolated to the EU setting. The less stable results from the European studies are explained by differencies in trial designs and inclusion criteria, with only few patients treated within 3 hours of onset. Further, the results of the published meta-analysis showed a tendency to go in the same direction as in the US trials, but patient numbers were too small for the efficacy endpoints to be statistically significant. In addition, it was emphasised that there is no such thing as a uniform European setting and that the differences between the health-care settings within the EU may be just as apparent as those between Europe and the US.

Following the publishing of the results of the meta-analysis many specialists consider data to be sufficient in support of treatment within 3 hours of onset. In addition, the experts consulted believe that it is possible in clinical practise to handle the product in accordance with the restrictions of the SPC in order to maximise the benefit. A placebo-controlled trial with a patient population as defined by the SPC and administration of alteplase within the 3-hour time window would therefore most likely

face difficulties with recruitment and may not be feasible. However, a similar study in the same patient population but within the time window 3-4 hours might be acceptable to EU investigators since it is generally considered to be a need of further efficacy and safety data here. This study design would allow extrapolation of results to the general stroke population, but the interpretation of results would be difficult in case of a negative outcome.

The Ad hoc Expert group agreed that the thrombolytic effect seems to be small or unclear in certain sub-populations such as patients with diabetes, patients with very severe stroke and in the elderly >75 years of age. The undertaking of placebo-controlled randomised clinical trials in special high-risk groups of patients, e.g. the elderly (>75 or >80 years) and within the 0-3 hour time-window, would be of general interest for the medical society as a whole. The demonstration of efficacy and safety in high-risk populations outside the SPC restrictions is considered both ethical and feasible. However, it would be difficult to extrapolate any results from such studies to the overall stroke population since a patient population similar to the original database in the US studies would be crucial for extrapolation.

The Ad hoc Expert group discussed the option of a randomised dose-comparator trial (with a clear null-hypothesis) within the 0-3 hour time window in order to explore the dose and gather additional confirmatory data. Feasibility was considered an issue in respect of patient recruitment due to ethical aspects relating to difficulties in defining the minimal effective dose and investigators' concern of randomising to a "pseudo-placebo". The group considered that such a study design might not provide the answers requested by the CPMP.

Oral explanation and further information provided by the Applicant on request by the CPMP:

The Applicant presented responses to the concerns raised during the assessment procedure at an oral explanation before the CPMP plenary on 23 April 2002. During the CPMP discussion that followed, the Committee considered an additional confirmatory European study necessary and a number of possible trial designs were discussed.

Following the CPMP request, the Company provided:
a) A final protocol for a randomised placebo-controlled confirmatory trial with reference to efficacy and safety to be undertaken in a wider time window e.g. 3-4 hours, with an appropriate sample-size and within a patient population identical to the SPC inclusion criteria/ the US NINDS trials *(ECASS-III study)*. In addition, a comprehensive list of centres to be included was provided.
b) Furthermore, the Company submitted a detailed proposal for a post-marketing surveillance strategy focusing on safety aspects (in particular intracranial haemorrhage and deaths) e.g. education and monitoring and a proposal for a risk management model predictive of which patients that may be at higher risk of bleeding. The Company has shown that a protocol to ensure a safe introduction of Actilyse on the EU market may be feasible.
c) The Company also provided a satisfactory protocol for the proposed European post-marketing surveillance study: 'SITS-MOST safety monitoring study'.

At the time of the CPMP opinion a couple of minor concerns related to the final protocols for the ECASS III and SITS-MOST studies remained, having no impact on the benefit/risk balance of the product. Therefore, the CPMP recommended that these should be dealt with by means of a post-opinion follow-up measure and should not pose a barrier to a positive opinion.

Risk/benefit evaluation:

Taking into account the the outcome and recommendations from the Ad Hoc Expert meeting of 22 April 2002, the overall information provided by the Marketing Authorisation Holder during the Actilyse arbitration procedure and the final revised SPC, the CPMP concluded that a Marketing Authorisation for alteplase for fibrinolytic treatment of acute ischaemic stroke where treatment is started within 3 hours of onset of the stroke symptoms and after prior exclusion of intracranial

haemorrhage by means of appropriate imaging techniques (see amended SPC), is considered acceptable, provided a confirmatory European study will be performed and appropriate commitments are made.

Therefore, during the CPMP discussions, the Committee considered the need to adopt, subject to conditions, a referral opinion for Actilyse.

Article 32.4 of Directive 2001/83/EC (previously Article 13.4 of Directive 75/319) provides the legal basis to require conditions, considered essential for the safe and effective use of the medicinal product including pharmacovigilance. On this basis, the CPMP required the Company to make the following commitments and required those commitments to be assessed on an annual basis by the Committee:

- The Company will perform a randomised placebo-controlled confirmatory trial with reference to efficacy and safety to be undertaken in a time window of 3-4 hours within a patient population identical to the SPC inclusion criteria / the US NINDS trials. Furthermore, the Company commits to provide detailed progress reports on the implementation of this study, including information on patient enrolment and follow-up on a bi-annual basis as of the date of the granting of the Commission Decision for the stroke indication, for review by the CPMP and in parallel to the submission of the PSURs. The study will start (defined as enrolment of first patient) within six months of the date of the granting of the Commission Decision and the final study report will be provided within six months after last patient out of the study.

- The Company will perform a European post-marketing surveillance study: "SITS-MOST safety monitoring study". Furthermore, the Company will provide detailed progress reports on the implementation of the study, including information on patient enrolment and follow-up on a bi-annual basis as of the date of the granting of the Commission Decision for the stroke indication, for review by the CPMP and in parallel to the submission of the PSURs. The study will start (defined as enrolment of first patient) within three months of the date of the granting of the Commission Decision and the final study report will be provided within six months after last patient out of the study.

- The Company will submit PSURs at 6-, 12-, 18-, 24 months, 3 years, 4 years and as part of the renewal application, as of the Commission Decision for the stroke indication.

- The final study protocols for the ECASS III and SITS-MOST studies will be submitted for review by the CPMP at the latest by 17 July 2002 (Commitment fulfilled: submitted by the Applicant and agreed by the Committee).

These conditions are annexed to the referral opinion/ Commission Decision and will form part of the marketing authorisations. As a consequence, the reassessment of the benefit/risk profile of Actilyse performed by the CPMP on the basis of those conditions will define the course of events that will have to be taken with regard to the marketing authorisation concerned.

In light of the commitments made by the Company and the agreed amendments to the SPC, the CPMP concludes that the risk/benefit ratio for alteplase appears positive for the claimed indication and posology.

The arbitration procedure resulted in the following conclusions:

- The results from the US trials may to some extent be extrapolated to the EU setting. The less stable results from the European studies are explained by differencies in trial designs and inclusion criteria, with only few patients treated within 3 hours of onset. Further, the results of the published meta-analysis showed a tendency to go in the same direction as in the US trials, but patient numbers were too small for the efficacy endpoints to be statistically significant.

- It is possible in clinical practise to handle the medicinal product in accordance with the restrictions of the amended SPC in order to maximise the treatment benefit.
- A placebo-controlled trial in a European setting with a patient population as defined by the amended SPC and administration of alteplase within the 3-hour time window would most likely face difficulties with recruitment and may not be feasible. However, a similar study in the same patient population but within the time window 3-4 hours might be acceptable to EU investigators since since it is generally considered to be a need for further efficacy and safety data here.
- Placebo-controlled randomised clinical trials in special high-risk groups of patients would be of general interest for the medical society as a whole and the demonstration of efficacy and safety in high-risk populations outside the SPC restrictions is considered both ethical and feasible. However, it would be difficult to extrapolate any results from such studies to the overall stroke population since a patient population similar to the original database in the US studies would be crucial for extrapolation.

A Marketing Authorisation for alteplase for fibrinolytic treatment of acute ischaemic stroke where treatment is started within 3 hours of onset of the stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques (see SPC), is therefore considered acceptable, provided appropriate commitments are made.

Article 32.4 of D 2001/83/EC (previously Article 13.4 of Directive 75/319) provides the legal basis to require conditions, considered essential for the safe and effective use of the medicinal product including pharmacovigilance. On this basis, the CPMP required the Company to make a number of commitments and required those commitments to be assessed on an annual basis by the Committee (see discussion on risk/benefit above).
The reassessment of the benefit/risk profile of Actilyse performed by the CPMP on the basis of those conditions will define the course of events that will have to be taken with regard to the marketing authorisation concerned.

Following the CPMP Ad Hoc Expert meeting and the oral explanations provided by the Company numerous amendments were made to the SPC. The proposed SPC is now considered to provide adequate information (see Annex I).

The CPMP having considered
- the MRP assessment report of the RMS,
- the issues for arbitration,
- the written responses provided by the Company,
- the Rapporteur/ Co-Rapporteur's assessment report on these responses, their joint reviews and the addendum to the final joint review,
- comments from the CPMP members,
- the conclusions and recommendations of the CPMP Ad Hoc Expert meeting,
- the oral explanations by the Company,
- and the commitments made by the Company,

was of the opinion that the questions by the Netherlands, Spain, Greece and the UK have been resolved. Since the risk/benefit ratio of alteplase in light of the conditions identified by the Committee and agreed by the Company is considered to be positive for the claimed indication and posology, a marketing authorisation should be granted. However, the SPC should be amended as set out in Annex III of the CPMP Opinion (see Annex I of this background document).

ANNEXES

Annex I - Amended Summary of Product Characteristics of the Reference Member State.

ANNEX I

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Note: This SPC was annexed to the Commission Decision on this referral for arbitration, and the text was valid at that time.

The SPC is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

Actilyse

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

The reconstituted solution contains 1 mg alteplase/ 1ml.

1 vial with 467 mg powder contains: 10 mg alteplase or
1 vial with 933 mg powder contains: 20 mg alteplase or
1 vial with 2333 mg powder contains: 50 mg alteplase or
1 vial with 4666 mg powder contains: 100 mg alteplase

Alteplase is produced by recombinant DNA technique using a Chinese hamster ovary cell-line. The specific activity of alteplase in-house reference material is 580.000 IU/mg. This has been confirmed by comparison with the second international WHO standard for t-PA. The specification for the specific activity of alteplase is 522.000 to 696.000 IU/mg.

The pH of the reconstituted solution is 7.3 +/- 0.5.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection and infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1.1. Thrombolytic treatment in acute myocardial infarction

- 90 minutes (accelerated) dose regimen (see posology and method of administration): for patients in whom treatment can be started within 6 h after symptom onset

- 3 h dose regimen (see posology and method of administration): for patients in whom treatment can be started between 6 - 12 h after symptom onset provided that the a.m. indication is clear

Actilyse has proven to reduce 30-day-mortality in patients with acute myocardial infarction.

4.1.2. Thrombolytic treatment in acute massive pulmonary embolism with haemodynamic instability.

The diagnosis should be confirmed whenever possible by objective means such as pulmonary angiography or non-invasive procedures such as lung scanning. There is no evidence for positive effects on mortality and late morbidity related to pulmonary embolism.

4.1.3. For fibrinolytic treatment of acute ischaemic stroke.

Treatment must be started within 3 hours of onset of the stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques.

4.2 Posology and method of administration

Actilyse should be given as soon as possible after symptom onset. The following dose guidelines apply.

Under aseptic conditions the content of an injection vial of Actilyse (10 or 20 or 50 or 100 mg) dry substance is dissolved with water for injections according to the following table to obtain either a final concentration of 1 mg alteplase/ml or 2 mg alteplase/ml:

For this the transfer cannulas provided with the packs of Actilyse 20 mg, Actilyse 50 mg and Actilyse 100 mg are to be used. In the case of Actilyse 10 mg a syringe should be used.

Actilyse vial		10 mg	20 mg	50 mg	100 mg
			Volume of Water for Injections		
Final concentration:			to be added to dry powder:		
(a) 1 mg alteplase/ml	(ml)	10	20	50	2 x 50
(b) 2 mg alteplase/ml	(ml)	5	10	25	50

The reconstituted solution should then be administered intravenously. It may be diluted further with sterile physiological saline solution (0.9 %) up to a minimal concentration of 0.2 mg/ml.

4.2.1. Myocardial infarction

a) 90 minutes (accelerated) dose regimen for patients with myocardial infarction, in whom treatment can be started within 6 hours after symptom onset:

	Concentration of alteplase 1 mg/ml	2 mg/ml
	ml	ml
15 mg as an intravenous bolus	15	7,5
50 mg as an infusion over 30 minutes	50	25
following by an infusion of 35 mg over 60 minutes, until the maximal dose of 100 mg	35	17,5

In patients with a body weight below 65 kg the dose should be weight adjusted according to the following table:

	Concentration of alteplase 1 mg/ml	2 mg/ml
	ml	ml
15 mg as an intravenous bolus	15	7,5
	ml/kg bw	ml/kg bw
and 0.75 mg/kg body weight (bw) over 30 minutes (maximum 50 mg)	0,75	0,375
followed by an infusion of 0.5 mg/kg body weight (bw) over 60 minutes (maximum 35 mg)	0,5	0,25

b) 3 h dose regimen for patients, in whom treatment can be started between 6 and 12 hours after symptom onset:

	Concentration of alteplase 1 mg/ml	2 mg/ml
	ml	ml
10 mg as an intravenous bolus	10	5
50 mg as an infusion over the first hour	50	25

	ml/30 min.	ml/30 min.
followed by infusions of 10 mg over 30 minutes, until the maximal dose of 100 mg over 3 hours	10	5

In patients with a body weight below 65 kg the total dose should not exceed 1.5 mg/kg.

The maximal accepted dose of alteplase is 100 mg.

Adjunctive therapy:
Acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued for the first months after myocardial infarction. The recommended dose is 160 - 300 mg/d.

Heparin should be administered concomitantly at least for 24 hours or longer (at least 48 hours with the accelerated dose regimen). It is recommended to start with an initial intravenous bolus of 5,000 IU prior to thrombolytic therapy and to continue with an infusion of 1,000 IU/hour. The dose of heparin should be adjusted according to repeated measurements of aPTT values of 1.5 to 2.5 fold of the initial value.

4.2.2. Pulmonary embolism

A total dose of 100 mg of alteplase should be administered in 2 hours. The most experience available is with the following dose regimen:

	Concentration of alteplase 1 mg/ml	2 mg/ml
	ml	ml
10 mg as an intravenous bolus over 1 – 2 minutes	10	5
followed by an intravenous infusion of 90 mg over 2 hours	90	45

The total dose should not exceed 1.5 mg/kg in patients with a body weight below 65 kg.

Adjunctive therapy:
After treatment with Actilyse heparin therapy should be initiated (or resumed) when aPTT values are less than twice the upper limit of normal. The infusion should be adjusted according to aPTT values of 1.5 to 2.5 fold of the initial value.

4.2.3. Acute ischaemic stroke

Treatment must be performed by a physician specialised in neurological care. (See contraindications and special warnings/ precautions for use.)

The recommended dose is 0.9 mg substance/kg body weight (maximum of 90 mg) infused intravenously over 60 minutes with 10% of the total dose administered as an initial intravenous bolus.

Treatment with Actilyse must be started within 3 hours of the onset of symptoms.

Adjunctive therapy:
The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of acetylsalicylic acid or intravenous heparin should be avoided in the first 24 hours after treatment with Actilyse. If heparin is required for other indications (e.g. prevention of deep vein thrombosis) the dose should not exceed 10,000 IU per day, administered subcutaneously.

4.3 Contraindications

Like all thrombolytic agents, Actilyse should not be used in cases where there is a high risk of haemorrhage such as:

- known haemorrhagic diathesis
- patients receiving oral anticoagulants, e.g. warfarin sodium.
- manifest or recent severe or dangerous bleeding
- known history of or suspected intracranial haemorrhage
- suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm
- any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- haemorrhagic retinopathy, e. g. in diabetes (vision disturbances may indicate haemorrhagic retinopathy)
- recent (less than 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel (e.g. subclavian or jugular vein puncture)
- severe uncontrolled arterial hypertension
- bacterial endocarditis, pericarditis
- acute pancreatitis
- documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial-aneurysm, arterial/venous malformations
- neoplasm with increased bleeding risk
- severe liver disease, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis.
- major surgery or significant trauma in past 3 month

4.3.1 Additional contraindications in acute myocardial infarction:
any history of stroke

4.3.2 Additional contraindications in acute pulmonary embolism:
any history of stroke

4.3.3 Additional contraindications in acute ischaemic stroke:

- symptoms of ischaemic attack began more than 3 hours prior to infusion start or when time of symptom onset is unknown,
- Minor neurological deficit or symptoms rapidly improving before start of infusion,
- Severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques,
- seizure at onset of stroke,
- evidence of intracranial haemorrhage (ICH) on the CT-scan,
- symptoms suggestive of subarachnoid haemorrhage, even if CT-scan is normal,
- administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory,
- patients with any history of prior stroke and concomitant diabetes
- prior Stroke within the last 3 months
- platelet count of below 100,000/mm^3
- systolic blood pressure > 185 or diastolic BP > 110 mm Hg, or aggressive management (IV medication) necessary to reduce BP to these limits
- blood glucose < 50 or > 400 mg/dl.

Use in children and elderly patients
Actilyse is not indicated for the treatment of acute stroke in children under 18 years or adults over 80 years of age.

4.4 Special warnings and special precautions for use

Thrombolytic/ fibrinolytic treatment requires adequate monitoring. Actilyse should only be used by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor that use.

The risk of intracranial haemorrhage is increased in elderly patients, therefore in these patients the risk/benefit evaluation should be carried out carefully.

As yet, there is only limited experience with the use of Actilyse in children.

As with all thrombolytic agents, the expected therapeutic benefit should be weighed up particularly carefully against the possible risk, especially in patients with :
- small recent traumas, such as biopsies, puncture of major vessels, intramuscular injections, cardiac massage for resuscitation
- conditions with an increased risk of haemorrhage which are not mentioned in chapter 4.3.

The use of rigid catheters should be avoided.

4.4.1 Additional special warnings and precautions in acute myocardial infarction:

A dose exceeding 100 mg of alteplase must not be given because it has been associated with an additional increase in intracranial bleeding.

Therefore special care must be taken to ensure that the dose of alteplase infused is as described in section 4.2 Posology and Method of Administration.

There is limited experience with readministration of Actilyse. Actilyse is not suspected to cause anaphylactic reactions. If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment initiated.

As with all thrombolytic agents, the expected therapeutic benefit should be weighed up particularly carefully against the possible risk, especially in patients with systolic blood pressure > 160 mm Hg.

4.4.2 Additional special warnings and precautions in acute pulmonary embolism:

Same as for acute myocardial infarction (4.4.1).

4.4.3 Additional special warnings and special precautions in acute ischaemic stroke ~~are~~:

Special precautions for use
Treatment must be performed only by a physician trained and experienced in neurological care.

Special warnings / conditions with a decreased benefit/risk ratio
Compared to other indications patients with acute ischaemic stroke treated with Actilyse have a markedly increased risk of intracranial haemorrhage as the bleeding occurs predominantly into the infarcted area. This applies in particular in the following cases:
- all situations listed in Section 4.3. and in general all situations involving a high risk of haemorrhage
- small asymptomatic aneurysms of the cerebral vessels
- patients pre-treated with acetyl salicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if Actilyse treatment is delayed. Not more than 0.9 mg alteplase/kg bodyweight (max. of 90 mg) should be administered in view of the increased risk of cerebral haemorrhage.

Patients treatment should not be initiated later than 3 hours after the onset of symptoms (see 4.3 contra-indications) because of an unfavourable benefit/risk ratio mainly based on the following:
- positive treatment effects decrease over time
- particularly in patients with prior ASA treatment the mortality rate increases
- risk increases with regard to symptomatic haemorrhages

A blood pressure (BP) monitoring during treatment administration and up to 24 hours seems justified; an i.v. antihypertensive therapy is also recommended if systolic BP > 180 mm Hg or diastolic BP < 105 mm Hg.

The therapeutic benefit is reduced in patients that had a prior stroke or in whom an uncontrolled diabetes is known, thus the benefit/risk ratio is considered less favourable, but still positive in these patients.

In patients with very mild stroke**,** the risks outweigh the expected benefit (see 4.3 contra-indications).

Patients with very severe stroke are at higher risk for intracerebral haemorrhage and death and should not be trated (see 4.3 contra-indications)**.**

Patients with extensive infarctions are at greater risk of poor outcome including severe haemorrhage and death. In such patients, the benefit/risk ratio should be thoroughly considered.

In stroke patients the likelihood of good outcomes decreases with increasing age, increasing stroke severity and increased levels of blood glucose on admission while the likelihood of severe disability and death or relevant intracranial bleedings increases, independently from treatment. Patients over 80, patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels < 50 mg/dl or >400 mg/dl at baseline should not be treated with Actilyse (see 4.3 contra-indications).

Other special warnings
Reperfusion of the ischaemic area may induce cerebral oedama in the infarcted zone.
Due to an increased haemorrhagic risk, treatment with platelet aggregation inhibitors should not be initiated within the first 24 hours following thrombolysis with alteplase.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of haemorrhage is increased if coumarine derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or LMWH or other agents inhibiting coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse) (see 4.3 contra-indications).

4.6 Pregnancy and lactation

There is very limited experience with the use of Actilyse during pregnancy and lactation. In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk.
In pregnant animals no teratogenic effects were observed after i.v. infusion of pharmacologically effective doses. In rabbits embryotoxicity (embryolethality, growth retardation) was induced by more than 3 mg/kg/day. No effects on peri-postnatal development or on fertility parameters were observed in rats with doses up to 10 mg/kg/day.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The most frequent adverse reaction associated with Actilyse is bleeding resulting in a fall in haematocrit and/or haemoglobin values. The type of bleeds associated with thrombolytic therapy can be divided into two broad categories:
- superficial bleeding, normally from punctures or damaged blood vessels,
- internal bleedings into the gastro-intestinal or uro-genital tract, retro-peritoneum or CNS or bleeding of parenchymatous organs.

Symptomatic intracerebral haemorrhage is the main adverse event of Actilyse in treatment of acute ischaemic stroke (up to 10% of patients).

In clinical studies with Actilyse significant blood-loss was observed occasionally from gastro-intestinal, uro-genital or retro-peritoneal bleeding. Ecchymosis, epistaxis and gingival bleeding are

observed rather frequently but usually do not require any specific action. In studies, where patients were treated according to clinical routine, i.e. without acute left-heart catheterisation, a blood transfusion was only occasionally necessary. In the treatment of acute myocardial infarction and acute pulmonary embolism intracranial haemorrhage was rarely reported (less than 1 %).

If a potentially dangerous haemorrhage occurs in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued. In general, however, it is not necessary to replace the coagulation factors because of the short half-life and the minimal effect on the systemic coagulation factors. Most patients who have bleeding can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement, and manual pressure applied to an incompetent vessel. Protamine should be considered if heparin has been administered within 4 hours of the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative.

Actilyse therapy may lead to cholesterol crystal embolisation or thrombotic embolisation in rare cases. In the organs concerned, this may lead to corresponding consequences (e.g. renal failure in the case of renal involvement).

In patients receiving Actilyse for myocardial infarction successful reperfusion is often accompanied by arrhythmias. These may require the use of conventional antiarrhythmic therapies.

Patients with myocardial infarction or pulmonary embolism may experience disease-related events such as cardiac failure, recurrent ischaemia, angina, cardiac arrest, cardiogenic shock, reinfarction, valve disorders (e.g. aortic valve rupture), and pulmonary embolism. These events have also been reported following thrombolytic therapy and can be life-threatening and may lead to death.

In rare cases nausea, vomiting, drop in blood pressure and increased temperature have been reported. These reactions can also occur as concomitant symptoms of myocardial infarction.

As with other thrombolytic agents, events related to the central nervous system (e.g. convulsions) have been reported in isolated cases, often in association with concurrent ischaemic or haemorrhagic cerebrovascular events.

In rare cases, anaphylactoid reactions have been reported. These are usually mild, but can be life-threatening in isolated cases. They may appear as rash, urticaria, bronchospasm, angio-oedema, hypotension, shock or any other symptom associated with allergic reactions. If they occur, conventional anti-allergic therapy should be initiated. Transient antibody formation to Actilyse has been observed in rare cases and with low titres, but a clinical relevance of this finding could not be established.

4.9 Overdose

The relative fibrin specificity notwithstanding, a clinical significant reduction in fibrinogen and other blood coagulation components may occur after overdosage. In most cases, it is sufficient to await the physiological regeneration of these factors after the Actilyse therapy has been terminated. If, however, severe bleeding results, the infusion of fresh frozen plasma or fresh blood is recommended and if necessary, synthetic antifibrinolytics may be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antithrombotic agent, ATC-code: B 01 A D 02

The active ingredient of Actilyse is alteplase, a glycoprotein, which activates plasminogen directly to plasmin. When administered intravenously, alteplase remains relatively inactive in the circulatory system. Once bound to fibrin, it is activated, inducing the conversion of plasminogen to plasmin leading to the dissolution of the fibrin clot.

In a study including more than 40,000 patients with an acute myocardial infarction (GUSTO) the administration of 100 mg alteplase over 90 minutes, with concomitant iv. heparin infusion, led to a lower mortality after 30 days (6.3 %) as compared to the administration of streptokinase, 1.5 million U over 60 minutes, with s.c. or iv. heparin (7.3 %). Actilyse-treated patients showed higher infarct related vessel patency rates at 60 and 90 minutes after thrombolysis than the streptokinase-treated patients. No differences in patency rates were noted at 180 minutes or longer.

30-day-mortality is reduced as compared to patients not undergoing thrombolytic therapy.

The release of alpha-hydroxybutyrate-dehydrogenase (HBDH) is reduced. Global ventricular function as well as regional wall motion is less impaired as compared to patients receiving no thrombolytic therapy.

Studies in myocardial infarction
A placebo controlled trial with 100 mg alteplase over 3 hours (LATE) showed a reduction of 30-day-mortality compared to placebo for patients treated within 6-12 hours after symptom onset. In cases, in which clear signs of myocardial infarction are present, treatment initiated up to 24 hours after symptom onset may still be beneficial.

Studies in pulmonary embolism
In patients with acute massive pulmonary embolism with haemodynamic instability thrombolytic treatment with Actilyse leads to a fast reduction of the thrombus size and a reduction of pulmonary artery pressure. Mortality data are not available.

Studies in acute stroke
In two USA studies (NINDS A/B) a significant higher proportion of patients, when compared to placebo, had a favourable outcome (no or minimal disability). These findings were not confirmed in two European studies and an additional USA study. In the latter studies however, the majority of patients were not treated within 3 hours of stroke onset. In a meta-analysis of all patients treated within 3 hours after stroke onset the beneficial effect of alteplase was confirmed. The risk difference versus placebo for a good recovery was 14.9% (CI 95% 8.1% to 21.7%) despite an increased risk of severe and fatal intracranial haemorrhage. The data do not allow drawing a definite conclusion on the treatment effect on death. Nevertheless overall, the benefit/risk of alteplase, given within 3 hours of stroke onset and taking into account the precautions stated elsewhere in the SPC, is considered favourable.

A meta-analyse of all clinical data show that, the agent is less effective in patients treated after 3 hours of onset (3 to 6 hours) compared with those treated within 3 hours of onset of symptoms, while the risks were higher, which makes the benefit/risk ratio of alteplase unfavourable outside the 0-3h time frame.

Due to its relative fibrin-specificity alteplase at a dose of 100 mg leads to a modest decrease of the circulating fibrinogen levels to about 60 % at 4 hours, which is generally reverted to more than 80 % after 24 hours. Plasminogen and alpha-2-antiplasmin decrease to about 20 % and 35 % respectively after 4 hours and increase again to more than 80 % at 24 hours. A marked and prolonged decrease of the circulating fibrinogen level is only seen in few patients.

5.2 Pharmacokinetic properties

Alteplase is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680 ml/min.). The relevant plasma half-life $T_{1/2}$alpha is 4-5 minutes. This means that

after 20 minutes less than 10% of the initial value is present in the plasma. For the residual amount remaining in a deep compartment, a beta-half-life of about 40 minutes was measured.

5.3 Preclinical safety data

In subchronic toxicity studies in rats and marmosets no unexpected side effects were found.
No indications of a mutagenic potential were found in mutagenic tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution:
L-arginine
Phosphoric acid, 10%,
Polysorbate 80

Solvent:
Water for injections

6.2 Incompatibilities

The reconstituted solution may be diluted further with sterile physiological saline solution (0.9 %) up to 1:5.

It may not, however, be diluted further with water for injections or carbohydrate infusion solutions, e. g. dextrose.

Actilyse must not be mixed with other drugs, neither in the same infusion-vial nor via the same catheter (not even with heparin).

6.3 Shelf life

36 months

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at
2 - 8°C and 8 hours at 25°C. From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C.
Protect from light. Store in the original package.

6.5 Nature and contents of container

Powder for solution:
10, 20, 50 or 100 ml sterilised glass vials, which are stoppered with sterile siliconised grey butyl-lyophilisation-type stoppers with aluminium/plastic flip-off caps.

Solvent:
The water for injections is filled into either 10, 20, 50 or 2 x 50 ml vials, depending on the size of the rt-PA vials. The water for injections vials are stoppered with appropriate rubber stoppers and aluminium/plastic flip-off type caps.

Transfer cannulas (included with pack-sizes of 20 mg, 50 mg and 100 mg only)

Pack sizes:

10 mg
1 vial with 467 mg powder for solution for infusion
1 vial with 10 ml of water for injections

20 mg
1 vial with 933 mg powder for solution for infusion
1 vial with 20 ml of water for injections
1 transfer cannula

50 mg
1 vial with 2333 mg powder for solution for infusion
1 vial with 50 ml of water for injections
1 transfer cannula

100 mg
1 vial with 4666 mg powder for solution for infusion
2 vials with 50 ml of water for injections
2 transfer cannulas

6.6 Instructions for use and handling

None

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Pharma KG
Binger Straße 173
55216 Ingelheim

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT