

EXPERT WORKING GROUP

ACTILYSE (A LTEPLASE) BALANCE OF BENEFITS AND RISKS WHEN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of paper: Paper 8: Risk minimisation measures

<p>Product: Actilyse 10, 20, 50mg</p>	<p>Assessors: Medical assessor: Dr [REDACTED] Scientific assessors: Dr [REDACTED] [REDACTED] Dr [REDACTED]</p>
<p>MAHs: Boehringer Ingelheim Limited</p>	<p>Previous Assessments: CHM May 2014 EWG: Nov 2014, Jan 2015</p>
<p>Active constituents: Alteplase (rt-PA)</p>	<p>Legal status: POM</p>
<p>Therapeutic classification: Antithrombotic agent, ATC code B01AD02</p>	

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1. Introduction

This paper discusses the current risk minimisation measures in place for rt-PA and their appropriateness and adequacy. Paper 9 discusses other communications documents and risk assessment tools that are currently in use, or planned, and the whether there is a need for further materials to aid clinical decision making and patient understanding of the benefits and risks of rt-PA treatment.

A distinction has been drawn between formal risk minimisation measures (measures that form part of the product's licence and which would therefore need to be agreed and applied in all member states where the mutual recognition authorisation is valid) and communications documents and other measures (information provided on a national basis, e.g. by the regulatory authority itself, or under a less formal agreement with the MAH, or by a professional body/patient organisation).

2. Current risk minimisation measures in place in the UK

The current risk minimisation measures in place for rt-PA are routine measures only, i.e. the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL). These documents are provided in Annex 2.

The MAH considers that there is no suggestion that these measures are insufficient and that there is no need for any additional measures to further improve the balance of benefits and risks of rt-PA. There is evidence that the difficulty of weighing stroke patients means that the dose of rt-PA administered is more often than not based on an estimate and further that the errors associated with such estimations may result in dosing errors. The MAH concludes that the clinical consequence of incorrect dosing remains controversial and that dosing errors have not been found to have a major impact on the risk of intracerebral haemorrhage.

The MAH's position is endorsed, however, it nevertheless remains possible that in some circumstances overdosing could lead to an increased risk of ICH and underdosing could reduce effectiveness. In an acute medical emergency it is not realistic to mandate the weighing of all patients and, perhaps in recognition of this, the national guidelines are silent on the issue of dosing.

The limited data that are available suggest that best practice could be to ensure that:

- stroke facilities have access to functioning weighing equipment that are suitable for supine patients and provide a rapid assessment of weight
- in the event that weighing the patient is not possible those who are not aphasic or obtunded should be asked their weight; where the patient is not capable of providing their weight, estimations should ideally be sought from family or carers; where this is not possible the consensus view of more than one healthcare professional should be used.
- all weights should be recorded in kg.

Such recommendations are not appropriate within a SmPC as a part of the product licence but could form part of clinical guidance. However, we have reviewed the SmPC to determine whether there are any other areas that could be clarified. In particular close attention was paid to the instructions for dilution and administration in stroke patients and a number of areas were identified that could be improved including:

- better use of headings and cross-referencing
- greater visibility of the 90mg maximum dose

- inclusion of a weight-based dosing table (which could also be made available more widely through the MAH website and in clinical guidance)

Detailed recommendations are provided in Annex 1.

The MAH also acknowledges the substantial off-label use in patients >80 years, but comments that this is occurring intentionally and not as a result of errors, and that it is in-line with current European and UK guidelines.

As discussed in paper 6 and 7, the MAH has stated that they are in the process of evaluating the benefits and risks of treatment with rt-PA in the population of >80 year olds. This will involve an analysis of all controlled randomised trials including IST-3, and the MAH intends that this will enable a definition of criteria for safe and effective treatment beyond the age of 80 years to be included as part of the product information. The MAH does not expect this update to expand the (combined on and off-label) use of rt-PA, and predicts that use overall may in fact decrease once the label defines which patients beyond the age of 80 are likely to benefit from treatment, as it may be necessary to restrict certain eligibility criteria for patients beyond 80 years.

The MAH has stated that they have no intentions to expand any other eligibility criteria, except for age.

3. Current national guidelines in the UK

The National Clinical Guideline for stroke (RCP, 2012) makes the following recommendations relating to treatment with rt-PA in the immediate management of non-haemorrhagic stroke:

- Any patient, regardless of age or stroke severity, where treatment can be started within 3 hours of known symptom onset and who has been shown not to have an intracerebral haemorrhage or other contraindications should be considered for treatment using alteplase.
- Between 3 and 4.5 hours of known stroke symptom onset, patients under 80 years who have been shown not to have an intracerebral haemorrhage or other contraindication, should be considered for treatment with alteplase.
- Between 3 and 6 hours of known stroke symptom onset, patients should be considered for treatment with alteplase on an individual basis, recognising that the benefits of treatment are likely to be smaller than those treated earlier, but that the risks of a worse outcome, including death, will on average not be increased.
- Alteplase should only be administered within a well-organised stroke service with:
 - staff trained in the delivery of thrombolysis and monitoring for post-thrombolysis complications
 - nurse staffing levels equivalent to those required in level 1 or level 2 nursing care with staff trained in acute stroke and thrombolysis
 - immediate access to imaging and re-imaging, and staff appropriately trained to interpret the images
 - processes throughout the emergency care pathway for the minimisation of in-hospital delays to treatment, to ensure that thrombolysis is administered as soon as possible after stroke onset

- protocols in place for the management of post-thrombolysis complications.

NICE guidelines on 'Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)' (2008) provide the following recommendation relating to rt-PA:

- Alteplase is recommended for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should only be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation.
- Alteplase should be administered only within a well organised stroke service with:
 - Staff trained in delivering thrombolysis and in monitoring for any complications associated with thrombolysis
 - Level 1 and level 2 nursing care staff trained in acute stroke and thrombolysis
 - Immediate access to imaging and re-imaging, and staff trained to interpret the images.
- Staff in A&E departments, if appropriately trained and supported, can administer alteplase for the treatment of acute ischaemic stroke provided that patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support.
- Protocols should be in place for the delivery and management of thrombolysis, including post-thrombolysis complications.

The European Stroke Organisation Guidelines for management of ischaemic stroke and TIA, 2008, which have not been updated since January 2009, make the following recommendations relating to rt-PA treatment:

- Intravenous rt-PA (0.9mg/kg body weight, maximum 90mg), with 10% of the dose given as a bolus followed by a 60-minute infusion, is recommended within 4.5 hours of onset of ischaemic stroke (Class 1, Level A), [*although treatment between 3 and 4.5 h is currently not included in the European labelling**].
- The use of multimodal imaging criteria may be useful for patient selection for thrombolysis but is not recommended for routine clinical practice (Class III, Level C)
- It is recommended that blood pressures of 185/110 mmHg or higher is lowered before thrombolysis (Class IV, GCP)
- It is recommended that intravenous rtPA may be used in patients with seizures at stroke onset, if the neurological deficit is related to acute cerebral ischaemia (Class IV, GCP)
- It is recommended that intravenous rtPA may also be administered in selected patients under 18 years and over 80 years of age, although this is outside the current European labelling (Class III, Level C)
- Intra-arterial treatment of acute MCA occlusion within a 6-hour time window is recommended as an option (Class II, Level B)

- Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients (Class III, Level B). Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 hours (Class III, Level B)
- It is recommended that aspirin (160–325 mg loading dose) be given within 48 hours after ischaemic stroke (Class I, Level A)
- It is recommended that if thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 hours (Class IV, GCP)
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischaemic stroke (Class III, Level C)
- The administration of glycoprotein-IIb-IIIa inhibitors is not recommended (Class I, Level A)
- Early administration of unfractionated heparin, low molecular weight heparin or heparinoids is not recommended for the treatment of patients with acute ischaemic stroke (Class I, Level A)
- Currently, there is no recommendation to treat ischaemic stroke patients with neuroprotective substances (Class I, Level A)

*no longer applicable

The national guidelines specific to the UK (National Clinical Guideline and NICE guidance) provide similar recommendations regarding the requirements of a stroke service appropriate for the administration of rt-PA. The NICE guidance provides less detail regarding the use of rt-PA in specific situations than the National Clinical Guideline, recommending that rt-PA is used in the treatment of acute ischaemic stroke, in full accordance with the marketing authorisation. The recommendations in the National Clinical Guideline that differ from the marketing authorisation are that:

- within 3 hours of stroke onset, patients of any age (i.e. including >80 years, and <18 years) or stroke severity (i.e. including severe and mild strokes) should be considered for treatment with rt-PA (but other contraindications should be followed)
- between 3 and 6 hours, patients should be considered for rt-PA treatment on an individual basis.

Therefore according to the National Clinical Guidelines, patients over 80 years of age should be considered for treatment with rt-PA within 3 hours of stroke onset, and whilst the guidance states that those patients <80 years should be considered for rt-PA treatment if they present between 3-4.5 hours (i.e. in-line with the licence), it is also stated that any patient can be considered for rt-PA treatment if they present between 3-6 hours following symptom onset – thereby allowing the treatment of patients >80 years beyond 3 hours following symptom onset.

A similar approach is taken by the ESO guidelines which state that rt-PA should be used in selected patients under 18 years and over 80 years.

The data available discussed in paper 6 indicate that in the UK, physicians are following the National Clinical Guidelines in terms of treatment of patients aged >80 years. It appears however that a more cautious approach is being taken with regards to the time to treatment, with few patients being treated beyond 4.5 hours after the onset of symptoms.

4. Discussion and conclusions

Paper 7 considered the current contraindications to treatment with rt-PA in acute ischaemic stroke. In general it was concluded that these restrictions are reasonable and possible to adhere to in UK clinical care. However it may be appropriate to re-evaluate the balance of benefits and risks of rt-PA in patients aged >80 years in light of the additional evidence available from the IST-3 trial. This subgroup was found to constitute the main off-label use of rt-PA in ischaemic stroke, and the available evidence did not raise concerns regarding this use. The MAH has confirmed that they are currently reviewing this subgroup of patients, with the intention of potentially submitting a variation within Europe to lift the contraindication. The MAH has noted that this review should better define which patients >80 years are appropriate for rt-PA treatment and in light of these findings it may be necessary to also introduce some restrictions to its use in this subgroup of patients.

If the variation to lift the contraindication in patients aged >80 is approved within Europe (including possible additional restrictions in this population) the total level of use of rt-PA in this group may decrease overall and the marketing authorisation for rt-PA would be more in-line with the National Clinical Guidelines. If restrictions are implemented to define which patients >80 years are suitable for rt-PA treatment, it may be possible for the guidelines to also be expanded to give further guidance in this group.

Paper 7 discussed the benefits and risks of rt-PA when used in clinical practice, and whether the SmPC reflects recent evidence. Whilst in the main, it was concluded that the SmPC contains appropriate contraindications and warnings, it is proposed that an additional warning should be added relating to increased risk of sICH after rt-PA treatment in patients with leukoaraiosis or other established brain lesions at stroke onset, and a further warning regarding the risk of deleterious synergistic effects of dual antiplatelet therapy as the risks of rt-PA therapy may outweigh any potential benefits in those receiving aspirin and clopidogrel if there are any additional adverse prognostic features (eg severe stroke, old age) (see paper 7 for further details).

As well as off label use, paper 7 considered evidence for the occurrence of inadvertent errors ('medication errors') with rt-PA in stroke. The data suggest that the main source of error is in the dosing and administering of rt-PA. This stems from the requirement for weight-based dosing and the inherent difficulties associated with weighing this population of patients. Where estimates of weight are provided, patients have been found to be the most accurate, followed by family/carers, and then healthcare professionals. In this regard, clinical guidance could be updated to provide advice for the weight estimation of stroke patients.

In addition, certain aspects of the dosing and administration instructions are not presented as clearly as they could be in the marketing authorisation and the MAH should be asked to make some amendments in line with the proposals in Annex 1. A key feature of this would be the inclusion of a weight-based dosing table.

In conclusion, the conditions for use of rt-PA for stroke thrombolysis as specified in the marketing authorisation appear to be evidence-based and feasible to adhere to in practice. Consequently, no urgent regulatory action is considered necessary to further improve the balance of risks and benefits of rt-PA in the indication of stroke. However, it is considered that further warnings could be provided regarding the increased risk of sICH in patients with leukoaraiosis or other established brain lesions at stroke onset and in patients taking dual anti-platelet therapy; and some aspects of the instructions for dosing and administration of rt-PA could benefit from clarification, including the provision of a weight-based dosing table. These amendments are not urgent and could be undertaken at the next routine regulatory opportunity.

Points for discussion by the EWG:

Does the EWG consider that it would be appropriate to update the SmPC with respect to the following:

- Warning of an increased risk of sICH after rt-PA treatment in patients with leukoaraiosis or other established brain lesions at stroke onset
- Warning that the risk of deleterious synergistic effects of dual antiplatelet therapy as the risks of rt-PA therapy may outweigh any potential benefits in those receiving aspirin and clopidogrel if there are any additional adverse prognostic features (e.g. severe stroke, old age)
- Inclusion of a weight-based dosing table
- Minor clarifications of the dosing and administration section?

Details of the proposals are provided in Annex 1.

Annex 1

Proposals for SmPC updates

Proposed text amendments in red

4.2 Posology and method of administration

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

Dosing instructions for all indications

Under aseptic conditions the content of an injection vial of Actilyse (10 mg or 20 mg or 50 mg) 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:

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

The reconstituted solution should then be administered intravenously. It may be diluted further with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg/ml. A dilution of the reconstituted solution with sterilised water for injections or in general, the use of carbohydrate infusion solutions, e.g. dextrose is not recommended. Actilyse should not be mixed with other medicinal products neither in the same infusion-vial nor the same catheter (not even with heparin). For further practical instructions for preparation and handling see sections 6.2 and 6.6.

The experience in children and adolescents is limited. Actilyse is contraindicated for the treatment of acute stroke in children and adolescents (see section 4.3).

Myocardial infarction

[...]

Pulmonary embolism

[...]

Acute ischaemic stroke

Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care, see sections 4.3 and 4.4.

Dilute Actilyse with water for injection to an initial concentration of 1mg/mL (see instructions above). The recommended dose is 0.9 mg alteplase/kg body weight – up to a (maximum of 90 mg) - infused intravenously over 60 minutes with 10% of the total dose administered as an initial intravenous bolus according to the following table:

	1	2	3	4	5
	Patient's weight (kg)	Equivalent Imperial weight	Bolus infusion mL	Infusion mL	Total dose (mg at 1 mg/mL)
One vial	35	5 st 6 lb	3	29	32
	40	6 st 4 lb	4	32	36
	45	7 st 1 lb	4	37	41
	50	7 st 12 lb	5	40	45
	55	8 st 9 lb	5	45	50
Two vials	60	9 st 6 lb	5	49	54
	65	10 st 3 lb	6	53	59
	70	11 st 0 lb	6	57	63
	75	11 st 11 lb	7	61	68
	80	12 st 8 lb	7	65	72
	85	13 st 5 lb	8	69	77
	90	14 st 2 lb	8	73	81
	95	14 st 13 lb	9	77	86
≥100	≥15 st 10 lb	9	81	90	

§ All volumes rounded up to the nearest whole number

Treatment with Actilyse must be started as early as possible within 4.5 hours of the onset of symptoms. Beyond 4.5 hours after onset of stroke symptoms there is a negative benefit risk ratio associated with actilyse administration and so it should not be administered (see section 5.1).

4.4 Special warnings and precautions for use

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:

- patients pre-treated with acetyl salicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if Actilyse treatment is delayed. This risk may be further increased in patients treated with the combination of aspirin and clopidogrel.

...

Other special warnings:

Data from a small number of observational studies indicates that the presence of severe leukoaraiosis on a baseline CT brain scan may increase the risk of intracerebral haemorrhage.

4.5 Interactions 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 active substances which interfere with coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse) (see section 4.3 and section 4.4).

6.2 Incompatibilities

The reconstituted solution may be diluted with sterile sodium chloride 9mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2mg alteplase per ml.

Further dilution, the use of water for injections for dilution or in general the use of carbohydrate infusion solutions, e.g. dextrose, is not recommended due to increasing formation of turbidity of the reconstituted solution.

Actilyse should not be mixed with other medicinal products neither in the same infusion vial nor the same catheter (not even with heparin).

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Actilyse 10mg
Powder and Solvent for Solution for Injection and Infusion

Actilyse 20mg
Powder and Solvent for Solution for Injection and Infusion

Actilyse 50mg
Powder and Solvent for Solution for Injection and Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial with powder contains:
10mg alteplase (corresponding to 5,800,000 IU) or
20mg alteplase (corresponding to 11,600,000 IU) or
50mg alteplase (corresponding to 29,000,000 IU), respectively

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.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection and infusion
The powder is presented as a colourless to pale yellow lyophilizate cake

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Thrombolytic treatment in acute myocardial infarction

- 90 minutes (accelerated) dose regimen (see section 4.2): for patients in whom treatment can be started within 6 h after symptom onset
- 3 h dose regimen (see section 4.2): for patients in whom treatment can be started between 6 - 12 h after symptom onset provided that the diagnosis has been clearly confirmed.

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

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.

Fibrinolytic treatment of acute ischaemic stroke

Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

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 mg or 20 mg or 50 mg) 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:

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

The reconstituted solution should then be administered intravenously. It may be diluted further with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2 mg/ml. A dilution of the reconstituted solution with sterilised water for injections or in general, the use of carbohydrate infusion solutions, e.g. dextrose is not recommended. Actilyse should not be mixed with other medicinal products neither in the same infusion-vial nor the same catheter (not even with heparin). For further practical instructions for preparation and handling see sections 6.2 and 6.6.

The experience in children and adolescents is limited. Actilyse is contraindicated for the treatment of acute stroke in children and adolescents (see section 4.3).

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
followed 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 maximum dose of alteplase is 100 mg.

Adjunctive therapy:

Antithrombotic adjunctive therapy is recommended according to the current international guidelines for the management of patients with ST-elevation myocardial infarction; acetylsalicylic acid should be initiated as soon as possible after symptom onset and continued with lifelong treatment unless it is contraindicated.

Pulmonary embolism

A total dose of 100 mg of alteplase should be administered in 2 hours. Most experience is available 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 to maintain aPTT between 50 - 70 seconds (1.5 to 2.5 fold of the reference value).

Acute ischaemic stroke

Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care, see sections 4.3 and 4.4.

The recommended dose is 0.9 mg alteplase/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 as early as possible within 4.5 hours of the onset of symptoms. Beyond 4.5 hours after onset of stroke symptoms there is a negative benefit risk ratio associated with actilyse administration and so it should not be administered (see section 5.1).

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

Generally in all indications Actilyse should not be administered to patients with known hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients listed in section 6.1.

Additional contraindications in acute myocardial infarction, acute pulmonary embolism and acute ischaemic stroke:

Actilyse is contraindicated in cases where there is a high risk of haemorrhage such as:

- significant bleeding disorder at present or within the past 6 months
- known haemorrhagic diathesis
- patients receiving effective oral anticoagulant treatment, e.g. warfarin sodium (see section 4.4)
- 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)
- 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 months.

Additional contraindications in acute myocardial infarction:

- any known history of haemorrhagic stroke or stroke of unknown origin
- known history of ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months, except current acute ischaemic stroke within 3 hours.

Additional contraindications in acute pulmonary embolism:

- any known history of haemorrhagic stroke or stroke of unknown origin
- known history of ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months, except current acute ischaemic stroke within 3 hours.

Additional contraindications in acute ischaemic stroke:

- symptoms of ischaemic attack beginning more than 4.5 hours prior to infusion start or symptoms for which the onset time is unknown and could potentially be more than 4.5 hours ago (see section 5.1)
- 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/mm³

- systolic blood pressure > 185 or diastolic BP > 110 mm Hg, or aggressive management (intravenous pharmacotherapy) necessary to reduce BP to these limits
- blood glucose < 50 or > 400 mg/dl.

Use in children and adolescents

Actilyse is not indicated for the treatment of acute stroke in paediatric patients under 18 years.

Use in elderly patients

Actilyse is not indicated for the treatment of acute stroke in adults over 80 years of age.

4.4 Special warnings and precautions for use

Special warnings and precautions in acute myocardial infarction, acute pulmonary embolism and acute ischaemic stroke:

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. It is recommended that when Actilyse is administered standard resuscitation equipment and pharmacotherapy be available in all circumstances.

Hypersensitivity

No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systemic experience with re-administration of Actilyse. Anaphylactoid reactions associated with the administration of Actilyse are rare and can be caused by hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. The stopper of the glass vial with Actilyse powder contains natural rubber (a derivative of latex) which may cause allergic reactions.

If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment initiated.

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 and adolescents.

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 section 4.3.

The use of rigid catheters should be avoided.

Patients receiving oral anticoagulant treatment:

The use of Actilyse may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely confirmed by appropriate test(s) of anticoagulant activity for the product(s) concerned showing no clinically relevant activity on the coagulation system (e.g. $INR \leq 1.3$ for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).

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.

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

GPIIb/IIIa antagonists:

Concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

Additional special warnings and precautions in acute pulmonary embolism:

same as for acute myocardial infarction (see above)

Additional special warnings and precautions in acute ischaemic stroke:

Special precautions for use:

Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular 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
- with later time-to-treatment from onset of stroke symptoms the net clinical benefit is reduced and may be associated with a higher risk of ICH and death compared to patients treated earlier. Therefore, the administration of Actilyse should not be delayed.
- patients pre-treated with acetyl salicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if Actilyse treatment is delayed..

Blood pressure (BP) monitoring during treatment administration and up to 24 hours seems justified; an intravenous 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 those with known uncontrolled diabetes, 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 section 4.3).

Patients with very severe stroke are at higher risk for intracerebral haemorrhage and death and should not be treated (see section 4.3).

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 section 4.3).

Data available from ECASS III and the pooled analysis indicate that the net clinical benefit becomes smaller in elderly with increasing age compared to younger patients as benefit from treatment with Actilyse appears to decrease and the risk of mortality appears to increase with increasing age.

Other special warnings:

Reperfusion of the ischaemic area may induce cerebral oedema 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

No formal interaction studies with Actilyse and medicinal products commonly administered in patients with acute myocardial infarction have been performed.

The risk of haemorrhage is increased if coumarine derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or LMWH or active substances which interfere with coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse) (see section 4.3). Concomitant treatment with ACE inhibitors may enhance the risk of suffering an anaphylactoid reaction, as in the cases describing such reactions a relatively larger proportion of patients were receiving ACE inhibitors concomitantly.

Concomitant use of GPIIb/IIIa antagonists increases the risk of bleeding.

4.6 Pregnancy and lactation

There is very limited experience with the use of alteplase during pregnancy and lactation. Studies in animals have shown reproductive toxicity (see section

5.3). In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk.

It is not known if alteplase is excreted into breast milk.

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

Except for intracranial haemorrhage as adverse reaction in the indication stroke and reperfusion arrhythmias in the indication myocardial infarction, there is no medical reason to assume that the qualitative and quantitative adverse reaction profile of Actilyse in the indications pulmonary embolism and acute ischaemic stroke is different from the profile in the indication myocardial infarction.

Haemorrhage

The most frequent adverse reaction associated with Actilyse is bleeding resulting in a fall in haematocrit and/or haemoglobin values:

very common:	bleeding from damaged blood vessels (such as haematoma) injection site haemorrhage (puncture site haemorrhage, catheter site haematoma, catheter site haemorrhage)
common:	intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation of stroke, intracranial haematoma, subarachnoid haemorrhage) in the treatment of acute ischaemic stroke. Symptomatic intracerebral haemorrhage represents the major adverse reaction in the treatment of acute ischaemic stroke (up to 10 % of patients without any increase of overall mortality and without any relevant increase in overall mortality and severe disability combined, i.e. mRS of 5 and 6). respiratory tract haemorrhage (such as pharyngeal haemorrhage, epistaxis, haemoptysis) gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, haemorrhage rectum, haematemesis, melaena, mouth haemorrhage, gingival bleeding) ecchymosis urogenital haemorrhage (such as haematuria, haemorrhage urinary tract) blood transfusion (necessary)
uncommon:	intracranial haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation of stroke, intracranial haematoma, subarachnoid haemorrhage) in the

treatment of acute myocardial infarction and acute pulmonary embolism
 ear haemorrhage
 haemopericardium
 retroperitoneal haemorrhage (such as retroperitoneal haematoma)
 rare: bleeding in parenchymatous organs (such as hepatic haemorrhage, pulmonary haemorrhage)
 very rare: eye haemorrhage
 Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

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.

Immune system disorders

uncommon: hypersensitivity reactions / anaphylactoid reactions (e.g. allergic reactions including rash, urticaria, bronchospasm, angio-oedema, hypotension, shock or any other symptom associated with allergic reactions)
 very rare: serious anaphylaxis

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.

Nervous system disorders

very rare: events related to the nervous system (e.g. epileptic seizure, convulsion, aphasia, speech disorder, delirium, acute brain syndrome, agitation, confusion, depression, psychosis) often in association with concurrent ischaemic or haemorrhagic cerebrovascular events

Cardiac disorders

As with other thrombolytic agents, the following events have been reported as sequelae of myocardial infarction and / or thrombolytic administration.

very common: recurrent ischaemia / angina, hypotension and heart failure / pulmonary oedema, reperfusion arrhythmias (such as arrhythmia, extrasystoles, AV block I° to complete, atrial fibrillation / flutter, bradycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia / fibrillation, electromechanical dissociation [EMD])
 common: cardiac arrest, cardiogenic shock and reinfarction
 uncommon: mitral regurgitation, pulmonary embolism, other systemic embolism / cerebral embolism, ventricular septal defect

These cardiac events can be life-threatening and may lead to death.

Vascular disorders

uncommon: embolism (thrombotic embolisation), which may lead to corresponding consequences in the organs concerned

Gastrointestinal disorders

common: nausea, vomiting

Investigations

very common: blood pressure decreased

common: body temperature increased

Injury and poisoning and procedural complications

rare: fat embolism (cholesterol crystal embolisation), which may lead to corresponding consequences in the organs concerned

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

Pharmacotherapeutic group: antithrombotic agent, ATC code: B 01 A D 02

The active ingredient of Actilyse is alteplase, a recombinant human tissue-type plasminogen activator, 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.

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.

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 intravenous 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

subcutaneous or intravenous 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.

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.

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.

Acute stroke

In two USA studies (NINDS A/B) a significant higher proportion of patients, had a favourable outcome with alteplase, compared to placebo (no or minimal disability). These findings were confirmed in the ECASS III trial (see paragraph below), after in the meantime two European studies and an additional USA study had failed to provide the respective evidence in settings essentially not compliant with the current EU product information.

The ECASS III trial was a placebo-controlled, double-blind trial conducted in patients with acute stroke in a time-window of 3 to 4.5 hours in Europe. Treatment administration in the ECASS III study was in line with the European SmPC for Actilyse in its stroke indication, except the upper end of the time of treatment window i.e. 4.5 hours. The primary end point was disability at 90 days, dichotomized for favourable (modified Rankin scale [mRS] 0 to 1) or unfavourable (mRS 2 to 6) outcome. A total of 821 patients (418 alteplase/403 placebo) were randomized. More patients achieved favourable outcome with alteplase (52.4%) vs. placebo (45.2%; odds ratio [OR] 1.34; 95% CI 1.02 - 1.76; P=0.038). The incidence of symptomatic intracranial haemorrhage was higher with alteplase vs. placebo (27.0% vs 17.6%, p=0.0012; Mortality was low and not significantly different between alteplase (7.7%) and placebo (8.4%; P=0.681). Subgroup results of ECASS III confirm that a longer OTT is associated with an increasing risk for mortality and symptomatic intracranial haemorrhage. The results of ECASS III show a positive net-clinical benefit for ACTILYSE® in the 3 to 4.5 hour time window, while pooled data demonstrate that the net-clinical benefit is no longer favourable for alteplase in the time window beyond 4.5 hours.

The safety and efficacy of ACTILYSE® for acute ischaemic stroke treatment up to 4.5 hours time *stroke onset time to start of treatment* (OTT) has been assessed by an ongoing registry (SITS-ISTR: The Safe Implementation of Thrombolysis in Stroke registry). In this observational study safety outcome data of 21.566 treated patients in the 0 to 3 hour time window were compared with data from 2.376 patients treated between 3 to 4.5 hours after onset of AIS. The incidence of symptomatic intracranial

haemorrhage (according to the SITS-MOST definition) was found to be higher in the 3 to 4.5 hour time window (2.2%) as compared with the up to 3 hour time window (1.7%). Mortality rates at 3 months were similar comparing the 3 to 4.5 hour time window (12.0%) with the 0 to 3.0 hours time window (12.3%) with an unadjusted OR 0.97 (95% CI: 0.84-1.13, p=0.70) and an adjusted OR 1.26 (95% CI: 1.07-1.49, p=0.005). The SITS observational data support clinical trial evidence of *stroke onset time to start of treatment* (OTT) as an important predictor of outcome following acute stroke treatment with alteplase.

5.2 P Pharmacokinetic properties

Alteplase is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550 - 680ml/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 undesirable effects were found. No indications of a mutagenic potential were found in mutagenic tests.

In pregnant animals no teratogenic effects were observed after intravenous infusion of pharmacologically effective doses. In rabbits embryotoxicity (embryolethality, growth retardation) was induced by more than 3mg/kg/day. No effects on peri-postnatal development or on fertility parameters were observed in rats with doses up to 10mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution:

Arginine

Phosphoric acid, dilute

Polysorbate 80

Solvent:

Water for injections

The pH of the reconstituted solution is 7.3 ± 0.5 .

6.2 Incompatibilities

The reconstituted solution may be diluted with sterile sodium chloride 9mg/ml (0.9 %) solution for injection up to a minimal concentration of 0.2mg alteplase per ml.

Further dilution, the use of water for injections for dilution or in general the use of carbohydrate infusion solutions, e.g. dextrose, is not recommended due to increasing formation of turbidity of the reconstituted solution.

Actilyse should not be mixed with other medicinal products neither in the same infusion vial nor the same catheter (not even with heparin).

6.3 Shelf life

10 mg, 20 mg and 50 mg pack sizes: 3 years

After reconstitution, an immediate use is recommended. However, the in-use stability has been demonstrated for 24 hours at 2°C-8°C and for 8 hours at 25°C.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution:

10ml, 20ml or 50ml sterilised glass vials, sealed with sterile siliconised grey butyl-type stoppers with aluminium/plastic flip-off caps.

Solvent:

The water for injections is filled into either 10ml, 20ml or 50ml vials, depending on the size of the powder vials. The water for injections vials are sealed with rubber stoppers and aluminium/plastic flip-off caps.

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

Pack sizes:

10mg:

1 vial with 467mg powder for solution for injection and infusion

1 vial with 10ml of water for injections

20mg:

1 vial with 933mg powder for solution for injection and infusion

1 vial with 20ml of water for injections

1 transfer cannula

50mg:

1 vial with 2333mg powder for solution for injection and infusion

1 vial with 50ml of water for injections

1 transfer cannula

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For reconstitution to a final concentration of 1mg alteplase per ml the full volume of solvent provided should be transferred to the vial containing the Actilyse powder. To this purpose a transfer cannula is included with the 20mg

and 50mg pack sizes, which is to be used. For the 10mg pack size a syringe should be used.

For reconstitution to a final concentration of 2mg alteplase per ml only half of the solvent provided should be used. In these cases always a syringe should be used to transfer the required amount of solvent to the vial containing the Actilyse powder.

A table giving the volumes of solvent required for reconstitution to the final concentrations for each pack size is provided in section 4.2.

When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation.

The reconstituted preparation is a clear and colourless to pale yellow solution. Prior to administration it should be inspected visually for particles and colour.

The reconstituted solution is for single use only. Any unused solution should be discarded.

7 MARKETING AUTHORITY AUTHORISATION HOLDER

Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS

8 MARKETING AUTHORITY AUTHORISATION NUMBER

PL 00015/0120

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/10/1988 / 26/04/2004

10 DATE OF REVISION OF THE TEXT

09/08/2013



PACKAGE LEAFLET: INFORMATION FOR THE USER

Actilyse® Powder and solvent for solution for injection and infusion 10 mg, 20 mg and 50 mg

alteplase

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. What Actilyse is and what it is used for
2. Before you receive Actilyse
3. How is Actilyse administered
4. Possible side effects
5. How to store Actilyse
6. Further information

1. WHAT ACTILYSE IS AND WHAT IT IS USED FOR

The active substance in Actilyse is alteplase (see section 6: "Further information"). It belongs to a group of medicines called thrombolytic agents. These medicines act by dissolving blood clots that have formed in blood vessels.

Actilyse is used to treat a number of conditions caused by blood clots forming within blood vessels, including:

- heart attacks caused by blood clots in the arteries of the heart (myocardial infarction)
- blood clots in the arteries of the lungs (pulmonary embolism)
- stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke)

2. BEFORE YOU RECEIVE ACTILYSE

Actilyse will not be given by your doctor

- if you are allergic (hypersensitive) to the active substance alteplase, to gentamicin (a trace residue from the manufacturing process), to natural rubber (also called latex which is part of the packaging material) or to any of the other ingredients of this medicine (listed in section 6)
- if you have, or have recently had, an illness that increases your risk of bleeding, including:
 - a bleeding disorder or tendency to bleed
 - a severe or dangerous bleed in any part of the body
 - bleeding within the brain or skull
 - uncontrolled, very high blood pressure
 - bacterial infection or inflammation of the heart (endocarditis), or inflammation of the membranes around the heart (pericarditis)
 - inflammation of the pancreas (acute pancreatitis)
 - gastric ulcer or ulcers in the gut
 - varicose veins in the gullet (oesophageal varices)
 - abnormalities of the blood vessels, such as a localised swelling of an artery (aneurysm)
 - certain tumours
 - severe liver disease
- if you are taking a medicine used to "thin" the blood (oral anticoagulants), unless appropriate tests confirmed no clinically relevant activity of such medicine
- if you have ever had surgery to your brain or spine
- if you have had major surgery or significant injury in the past 3 months
- if you have been given external heart massage in the past 10 days
- if you have had a baby in the past 10 days

Your doctor will also not use Actilyse for the treatment of heart attacks or blood clots in the arteries of the lungs

- if you have or have ever had a stroke caused by bleeding in the brain (haemorrhagic stroke)
- if you have or have ever had a stroke of unknown cause
- if you have recently (in the past 6 months) had a stroke caused by a blood clot in an artery of the brain (ischaemic stroke), unless this is the stroke you are about to be treated for

In addition your doctor will not use Actilyse for the treatment of a stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke)

- if the symptoms of your stroke began more than 4.5 hours ago or if it may be possible that the symptoms began more than 4.5 hours ago, because you do not know when they began
- if your stroke is causing only very mild symptoms
- if there are signs of bleeding in the brain
- if you have had a stroke within the last three months
- if the symptoms are rapidly improving before receiving Actilyse
- if you have a very severe stroke
- if you had cramps (convulsions) when your stroke started
- if your thromboplastin time (a blood test to see how well your blood clots) is abnormal. This test can be abnormal if you have received heparin (a medicine used to "thin" the blood) within the previous 48 hours
- if you are diabetic and have ever had a stroke before
- if the number of blood platelets (thrombocytes) in your blood is very low
- if you have a very high blood pressure (above 185/110) which can only be reduced by injection of medicines
- if the amount of sugar (glucose) in your blood is very low (under 50 mg/dl)
- if the amount of sugar (glucose) in your blood is very high (over 400 mg/dl)
- if you are under 18 years or over 80 years of age



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Ingelheim

Your doctor will take special care with Actilyse

- if you have had any allergic reaction other than a sudden life-threatening allergic reaction (severe hypersensitivity) to the active substance alteplase, to gentamicin (a trace residue from the manufacturing process), to natural rubber (also called latex which is part of the packaging material) or to any of the other ingredients of this medicine (listed in section 6)
- if you have or have recently had any other conditions that increase your risk of bleeding, such as:
 - small injury
 - biopsy (a procedure for obtaining a tissue specimen)
 - puncture of major vessels
 - intramuscular injection
- if you have ever received Actilyse before
- if you are over 65 years of age

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is particularly important that you tell your doctor if you are taking or have recently taken:

- any medicines which are used to "thin" the blood, including:
 - aspirin
 - warfarin
 - coumarin
 - heparin
- certain medicines used to treat high blood pressure (ACE inhibitors)

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine. Your doctor will only give you Actilyse if the possible benefit outweighs the possible risk to your baby.

3. HOW IS ACTILYSE ADMINISTERED

Actilyse will be administered to you by your doctor or by a health care professional. It is not for self-administration.

Treatment with Actilyse should be initiated as soon as possible after the start of your symptoms.

There are three different conditions for which this medicine can be given:

Heart attack (myocardial infarction)

The dose you are given depends on your body weight. The maximum dose of Actilyse is 100 mg but will be lower if you weigh less than 65 kg. It can be administered in two different ways:

- a) The 90 minute form of administration, for patients treated within 6 hours after start of their symptoms. This consists of:
 - an initial injection of part of the dose of Actilyse into a vein
 - infusions of the remainder of the dose over the following 90 minutes
- b) The 3 hour form of administration, for patients treated 6 to 12 hours after start of their symptoms. This consists of:
 - an initial injection of part of the dose of Actilyse into a vein
 - infusions of the remainder of the dose over the following 3 hours

In addition to Actilyse your doctor will give you another medicine to stop the blood clotting. This will be given as soon as possible after your chest pain starts.

Blood clots in the arteries of the lungs (pulmonary embolism)

The dose you are given depends on your body weight. The maximum dose of Actilyse is 100 mg but will be lower if you weigh less than 65 kg. The medicine is usually given as:

- an initial injection of part of the dose into a vein
- an infusion of the remainder of the dose over the following 2 hours

After the treatment with Actilyse, your doctor will start (or resume) therapy with heparin (a medicine to "thin" the blood).

Stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke)

Actilyse must be given within 4.5 hours of the first symptoms. The earlier you receive Actilyse, the more you can benefit from the treatment and the less likely are harmful side effects to occur. The dose you are given depends on your body weight. The maximum dose of this medicine is 90 mg but will be lower if you weigh less than 100 kg. Actilyse is given as:

- an initial injection of part of the dose into a vein
- an infusion of the remainder of the dose over the following 60 minutes

You should not take aspirin for the first 24 hours after your treatment with Actilyse for a stroke. Your doctor may give you an injection with heparin if this is necessary.

Method of administration

Actilyse is supplied as a powder and solvent for solution for injection or infusion. This means that each pack contains one vial with powder and one vial with the solvent (water for injections). Before use, the solvent is added to the powder to form a solution ready for administration. This solution is given into a vein (intravenous injection or infusion).

Actilyse should not be mixed with other medicines.

If you have any further questions on the use of Actilyse, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Actilyse can cause side effects, although not everybody gets them. The side effects described below have been experienced by people given Actilyse. Your treatment may be stopped by your doctor if any of the following side effects occur:

- bleeding in the brain (cerebral haemorrhage) after the treatment of a stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke)
- cessation of heartbeat (cardiac arrest)
- shock (a very low blood pressure) due to heart failure
- bleeding in the respiratory tract, such as nosebleeds (epistaxis) or blood stained phlegm (haemoptysis)
- bleeding in the brain (cerebral haemorrhage) after the treatment of heart attacks (myocardial infarction) or blood clots in the arteries of the lungs (pulmonary embolism)
- bleeding into the membranous sac surrounding the heart (haemopericardium)
- internal bleeding into the back part of the abdomen (retroperitoneal bleeding)
- damage to the heart valves (mitral regurgitation) or to the wall dividing the heart chambers (ventricular septal defect)
- bleeding in internal organs, e.g. bleeding in the liver (hepatic haemorrhage) or in the lung (pulmonary haemorrhage)
- formation of cholesterol crystal clots which can travel to other organs in the body (cholesterol crystal embolisation). The symptoms will depend on the organ affected
- serious allergic reaction (e.g. life-threatening anaphylaxis, difficulty breathing (bronchospasm), fluid under the skin (angioedema), low blood pressure or shock)
- heart failure

The following are other possible side effects that may cause your doctor to stop your treatment but, this will depend on how severe the side effects are:

Very common (occurs in more than 1 in 10 patients receiving the medicine)

- fluid on the lungs (pulmonary oedema)
- bleeding or bruising (haematoma) where the injection is given
- low blood pressure (hypotension)
- irregular heart beat after the blood supply to the heart has been restored
- chest pain (angina pectoris)

Common (occurs in less than 1 in 10 patients receiving the medicine)

- further heart attack
- bleeding of the gums
- bleeding in the stomach or gut, including vomiting blood (haematemesis) or blood in the stools (melana or rectal haemorrhage)
- bleeding into the body tissues causing purplish bruising (ecchymosis)
- bleeding from the urinary tract or the reproductive organs, which may lead to blood in your urine (haematuria)
- bleeding which necessitates a blood transfusion
- feeling sick (nausea)
- vomiting
- fever

Uncommon (occurs in less than 1 in 100 patients receiving the medicine)

- bleeding from the ear
- formation of blood clots in the lungs (pulmonary embolism)
- formation of blood clots in the blood vessels which can travel to other organs in the body (thrombotic embolisation). The symptoms will depend on the organ affected
- allergic reactions, e.g. hives (urticaria) and rash

Very rare (occurs in less than 1 in 10,000 patients receiving the medicine)

- bleeding in the eyes (ocular haemorrhage)
- events which affect the nervous system such as:
 - cramps (convulsions, fits)
 - speech problems
 - confusion or delirium (very severe confusion)
 - anxiety accompanied by restlessness (agitation)
 - depression
 - altered thinking (psychosis)

These disorders often occur in association with a stroke caused by a blood clot or bleeding in the brain.

Tell your doctor immediately if you think you are experiencing any of the side effects.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE ACTILYSE

Keep out of the reach and sight of children.

Actilyse should not be used after the expiry date which is stated on the vial label and the carton. The expiry date refers to the last day of that month.

Normally you will not be asked to store Actilyse as it will be given to you by your doctor. Do not store above 25°C. Store in the original package in order to protect from light.

Once the solution is ready for administration, it should be used immediately. The solution may be stored for 24 hours at 2°C - 8°C or for 8 hours at up to 25°C.

6. FURTHER INFORMATION

What Actilyse contains

- The active substance is alteplase. Each vial contains 10 mg (corresponding to 5,800,000 IU), 20 mg (corresponding to 11,600,000 IU) or 50 mg (corresponding to 29,000,000 IU) alteplase. Alteplase is produced recombinant DNA technique using a Chinese hamster ovary cell-line
- The other ingredients are arginine, phosphoric acid (dilute) and polysorbate 80
- The solvent is water for injections
- The rubber stopper of the packaging material contains natural rubber (latex)

What Actilyse looks like and contents of the pack

Actilyse is a powder and solvent for solution for injection and infusion. This means that each complete pack contains one vial with powder and one vial with the solvent.

Actilyse is available in the following pack sizes:

- One vial of powder with 10 mg alteplase and one vial with 10 ml solvent
- One vial of powder with 20 mg alteplase, one vial with 20 ml solvent and one transfer cannula
- One vial of powder with 50 mg alteplase, one vial with 50 ml solvent and one transfer cannula

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Boehringer Ingelheim Limited,
Ellesfield Avenue,
Bracknell,
Berkshire, RG12 8YS
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Manufacturer

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EXPERT WORKING GROUP

ACTILYSE (ALTEPLASE) BALANCE OF BENEFITS AND RISKS WHEN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of paper: Paper 10: Draft conclusions and recommendations to CHM and strategy for communication of the outcome of the group

<p>Product: Actilyse 10, 20, 50mg</p>	<p>Assessors: Medical assessor: Dr [REDACTED] Scientific assessor: Dr [REDACTED] Statistical assessor: Dr [REDACTED] Epidemiological assessors: Dr [REDACTED] Dr [REDACTED]</p>
<p>MAHs: Boehringer Ingelheim Limited</p>	<p>Previous Assessments: CHM May 2014 EWG: Nov 2014, Jan 2015</p>
<p>Active constituents: Alteplase (rt-PA)</p>	<p>Legal status: POM</p>
<p>Therapeutic classification: Antithrombotic agent, ATC code B01AD02</p>	

1. Introduction

In May 2014 the Commission on Human Medicines (CHM) considered the MHRA assessment of new data and specific concerns that had been raised regarding the use of rt-PA in the treatment of acute ischaemic stroke. CHM concluded that the data presented did not change the balance of benefits and risks for rt-PA in the treatment of acute ischaemic stroke. However, in order to be assured that all relevant sources of evidence had been taken into consideration, CHM also advised that an expert working group should be set up.

The Terms of Reference for the group were agreed at the first EWG meeting, as follows:

The terms of reference for the Expert Working Group were agreed at the first meeting in November 2014:

The Expert Working Group on rt-PA will:

- review all sources of evidence on efficacy and safety of alteplase in clinical use in ischaemic stroke
- advise whether these data have implications for the benefit:risk of alteplase in clinical use for the treatment of ischaemic stroke
- consider whether further measures are necessary to minimise harm in stroke patients
- advise on a communication strategy

This paper captures the draft conclusions and recommendations of the Group on the basis of evidence heard at the first two meetings. It also summarises the information in the papers for this third and final meeting and sets out the conclusions and recommendations of those papers.

The Group is asked to particularly note that this paper will be updated in accordance with the conclusions and recommendations that are agreed at this meeting. A final updated version of the paper will be circulated to the Group for agreement after the meeting and before it is presented to CHM.

2. Data considered by the Expert Working Group

The rt-PA expert working group has met twice, in November 2014 and January 2015, with third and final meeting taking place in June 2015. The evidence considered by the group has been provided in a series of papers, as follows:

Paper 1: Introduction to the papers and background to the current situation (1st meeting)

Paper 1A: Regulatory history of rt-PA use in acute ischaemic stroke. This paper provided further background information regarding the evidence behind the initial approval of rt-PA in the indication of acute ischaemic stroke, and the subsequent extension to the time-window for treatment to 4.5 hours post-symptom onset. (2nd meeting)

Paper 2: Stroke care in the UK and a wider perspective since 2000. This paper provided a description of the changes in stroke care in the UK that have taken place during the current and last decade and the impacts of these changes on morbidity and mortality of stroke patients. The paper also considers whether there is evidence for a learning curve within stroke centres and the imaging techniques used in the

diagnosis of acute stroke patients and whether there is evidence to support any change to the current product information or clinical guidelines. (1st meeting)

Paper 3: Usage of rt-PA. This paper provides information relating to the level of use of rt-PA in the UK and more widely, including off-label use. (1st meeting)

Paper 4: Benefits and risks: new study data. This paper provides a summary of the main clinical trial data that supported the initial approval of the acute ischaemic stroke indication and the extension to the time-window to 4.5 hours post-symptom onset. The paper also discusses data that have not previously been considered, including the latest data from SITS-ISTR, the SITS-UTMOST cohort, the Get With The Guidelines-Stroke registry, the Bade-Wuerttemberg Stroke registry, and the Canadian Alteplase for Stroke Effectiveness Study. (1st meeting)

Paper 4A: Benefits and risks: new study data - Addendum 1: This paper provides an assessment of the final report of the SITS-UTMOST registry. (3rd meeting)

Paper 5: Discussion of individuals' concerns on specific aspects of the supporting clinical evidence. This paper addresses specific concerns that have been raised with MHRA in three submissions, from Dr ██████████ Dr Mandava and Professors Fatovich and Brown. Dr ██████████ and Professors Fatovich and Brown have raised a wide variety of concerns relating to the key clinical trials, and Dr Mandava has provided data regarding the analysis methods used in clinical trials of acute stroke. In addition this paper discusses the definitions of symptomatic intracerebral haemorrhage used in clinical trials and the choice of primary endpoint and analysis method. (1st and 2nd meetings)

Paper 5A: Additional submissions received from interested parties. This paper discussed the submission of a (then unpublished) article by Dr Alper which concluded that rt-PA should not be recommended beyond 3 hours after stroke onset outside of clinical trials. Submissions from the British Association of Stroke Physicians, British Geriatrics Society, Association of British Neurologists, Royal College of Radiologists and the Royal College of Physicians were also considered. These recommended articles for consideration by the EWG which have been discussed in other papers. (2nd meeting)

Paper 5B: Additional information on individuals' concerns on specific aspects of the supporting clinical evidence. This paper follows up on a concern raised by Dr ██████████ relating to the appearance of reconstituted rt-PA compared with placebo and the potential for unblinding. It also provides some further information on the arginine excipient and a further submission from the British Geriatrics Society. (3rd meeting)

Paper 5C: Further submission by Dr ██████████ The main concerns assessed in this paper are that key data relating to the effectiveness of rt-PA on cerebral ischaemia and infarction have not been adequately presented in study publications and that a number of systematic reviews and meta-analyses have recycled incomplete data over the last 5 years to provide reassuring evidence on the benefit-risk balance of rt-PA. The other main area of concern is early mortality rates due to cerebral oedema. (3rd meeting)

Paper 5D: Benefit:risk of rt-PA administered between 3-4.5 hours. This paper provides a summary and discussion of the balance of benefits and risks of rt-PA in the 3-4.5 hour time-window. (3rd meeting)

Paper 6: Clinical use of rt-PA in the UK and feasibility of treating within the conditions of the marketing authorisation. (3rd meeting)

Paper 7: Benefits and risks of rt-PA in clinical practice, including in off-label use, and the occurrence of medication errors. This paper considers whether specific patient sub-groups are appropriately reflected in the relevant sections of the current SmPC,

including consideration of contraindicated populations and the occurrence of medication errors. (3rd meeting)

Paper 8: Risk minimisation measures. This paper discusses the current formal risk minimisation measures in place for rt-PA, their appropriateness and adequacy. (3rd meeting)

Paper 9: Communication of risk and benefit to patients. This paper discusses the current national communications and risk estimation/decision tools, and whether there is a need for further materials to aid decision making or understanding of benefits and risks of rt-PA. It provides suggestions for information resources that may be helpful to patients/families and clinicians. (3rd meeting)

Paper 10: - Draft conclusions and recommendations to CHM and strategy for communication of the outcome of the group. This paper attempts to summarise the conclusions of the group to date and provides draft conclusions and recommendations for the final meeting. (3rd meeting)

CHM paper, May 2014: This paper was provided to the EWG as background information regarding the issue, including assessment of new data and of initial concerns raised by Dr [REDACTED]. (1st meeting)

The EWG has also heard presentations from:

- Professor Jonathan Emberson on the STT individual patient meta-analysis published in 2014 (1st meeting)
- Professor Gary Ford on his experience of rt-PA and in particular the SITS registry (1st meeting)
- Dr [REDACTED] on his concerns regarding the benefits and risks of rt-PA in the treatment of acute ischaemic stroke (1st meeting)
- Professor Peter Sandercock on the IST-3 trial and results and his personal experience with rt-PA (2nd meeting)
- Professor Colin Baigent on further analyses of the STT dataset (2nd meeting)
- Professor Keith Muir on the definitions and implications of symptomatic intracranial haemorrhage (2nd meeting)

Additional presentations are planned for the June meeting of the EWG, including an update from Professor Baigent regarding additional analyses of the STT dataset, a presentation by Dr Gillian Cluckie on communications between clinicians and patients/families during an acute stroke event and a presentation from Professor Ford and Dr Peter McMeekin on the COMPASS model and its development and validation.

3. Draft conclusions

This section provides draft conclusions from the EWG meetings which will form the basis of the recommendations to CHM. These will be discussed and revised as necessary during the third and final meeting.

Prognosis of stroke in the UK following the introduction of rt-PA

The Group was asked to consider whether the introduction of rt-PA for the treatment of stroke had had any noticeable impact on stroke outcome in the UK.

The Group considered that there are compelling data to suggest that the prognosis of patients with ischaemic stroke had improved in the last decade and the latest mortality data suggested improved outcomes compared with previously. However, the reasons behind these improvements are difficult to ascertain given the many organisational changes that have taken place as a result of the introduction of rt-PA. Furthermore the overall net beneficial effects of the introduction of rt-PA are likely to be small as a result of the small proportion of patients who are eligible for rt-PA treatment.

Radiological diagnosis

In light of advances in radiological diagnostic techniques for stroke the evidence was evaluated to determine if CT scanning, which is currently recommended in the SmPC, remained the optimal diagnostic method.

The Group discussed the imaging methods used in acute ischaemic stroke, noting that non-enhanced CT imaging had been used in all randomised controlled trials, and concluded that there was no evidence to support other methods making a significant difference. CT imaging was considered to be universally accessible, tolerable, quick to perform and excluded haemorrhagic stroke with almost 100% sensitivity. Where uncertainty remains following CT scanning, the Group considered that diffusion weighted MRI imaging techniques would be more sensitive, for example in those with minor strokes.

The group concluded that there was insufficient evidence to suggest that another form of radiological detection, including MRI, should be used routinely instead of CT scanning.

New data since extension of the time window to 4.5 hours

The Group noted the data that had become available from clinical trials and observational studies since the time-window for treatment with rt-PA was increased from 3 to 4.5 hours. The Group discussed the SITS registry data following a presentation by Professor Gary Ford. The Group noted that the publication of SITS data and ECASS III appeared to have resulted in increased confidence in rt-PA, resulting in increased use in both the <3 hour time-window and the 3-4.5 hour time-window.

The Group also discussed the IST-3 trial results, following a presentation from Professor Peter Sandercock. The Group noted that the design of the IST-3 trial was such that patients were enrolled only if the clinician was uncertain whether to treat or not; the patient group included would therefore be expected to be at higher risk than patients included in previous clinical trials and treated in the clinic. The Group noted that the relative risk of sICH varied little between different patient subgroups, although the absolute risk did vary e.g. with stroke severity. The Group noted that the balance of benefits and risks in patients with mild stroke was less clear than in patients with more severe stroke but that IST-3 was underpowered in mild stroke and that ongoing clinical trials in this contraindicated population should provide further information.

The Group discussed the recent STT individual patient data meta-analysis (Emberson et al, 2014) following a presentation by Professor Jonathan Emberson. In particular the Group noted that all analyses were consistent with better outcomes at shorter time to onset of treatment. The Group was also reassured that all definitions of 'good outcome', in terms of where the endpoint (mRS) had been dichotomised, found a beneficial effect with rt-PA. In addition, the Group noted that the effect on

mortality by rt-PA was due to the initial risk of fatal ICH, and rt-PA did not impact on other causes of death. The signal of ICH found in the meta-analysis was as expected.

The Group concluded that overall the new data did not provide any new evidence of harm or lack of benefit with rt-PA.

Concerns of clinicians on the data

The Group considered a detailed evaluation of the concerns of a number of clinicians on the supporting clinical evidence. A wide variety of issues were raised, relating to the initial trials in animals, data with streptokinase, concerns regarding specific clinical trials (NINDS, ECASS I, II and III, ATLANTIS and IST-3), in addition to more general concerns regarding appropriateness of endpoints used in clinical trials and the impact of baseline imbalances on the results of the key studies. In particular, the existence of baseline imbalance in stroke scores in the NINDS trial was raised together with the different interpretations of the NINDS results (including the graphical analysis by Hoffman), the distribution of the time to treatment in NINDS, the potential for bias in IST-3, information on cerebral oedema, and concern that the evidence for a positive balance of benefits and risks in the 3-4.5 hour time-window is inadequate.

The Group also heard a presentation by Dr [REDACTED]. The Group discussed the points raised at length and whilst there were substantial concerns over various aspects of the analyses presented it was agreed that some important issues had been highlighted that merited further evaluation.

Additional analyses conducted by the STT group were presented to the Group by Professor Colin Baigent. The Group noted that formal tests had demonstrated that the IST-3 trial data were consistent with the other trials, and that no trial had been found to be an outlier. The Group noted that the effects of age, treatment delay and baseline stroke severity strongly interacted and that multivariable regression analysis of the data was therefore necessary. The analyses found that younger patients presented later, that older patients had more severe strokes and that less severe strokes were more likely to be randomised later. The Group heard that when the data from NINDS was removed from the meta-analysis, the results were qualitatively the same, although less robust because NINDS was a positive trial.

On the basis of the evidence presented the Group considered that the evidence for benefit with treatment up to 3 hours post symptom onset was very clear and that minimising the time to onset of treatment was critical to ensuring the best possible outcome. The evidence for treatment between 3-4.5 hours was considered to be more complicated as the benefit is reduced and this sub-group of patients are more heterogeneous in their characteristics. In particular the Group considered that the benefit-risk balance was less clear-cut for patients with mild stroke treated in the 3-4.5 hour time-period and noted that rt-PA is contraindicated in this population.

Feasibility of using rt-PA within the terms of the licence

The Group noted that data from SITS suggests that ~70% of use of rt-PA is within the conditions of the marketing authorisation, and that most of the off-label use occurs in patients aged >80 years (SITS registry data suggested that ~29% of patients were aged over 80 years). Only a small proportion of patients appear to be treated beyond 4.5 hours. Use in patients over 80 years of age is supported by the National Clinical Guidelines and therefore this finding was not unexpected.

The contraindications for treatment with rt-PA are fairly extensive and therefore this inevitably raises questions regarding the feasibility of complying with all of these conditions when it is essential that treatment is administered as quickly as possible.

Overall it was concluded that it is likely that in many cases it will not be possible to obtain every relevant piece of information and still treat the patient in the shortest possible time. Therefore it is expected that physicians would apply their clinical judgement regarding the need for particular investigations prior to administration of rt-PA. The Group concluded that it remains appropriate to include all relevant contraindications, as different pieces of information will be available for different patients.

Balance of benefits and risks in different patient populations

The Group considered the balance of benefits and risks in various patient subgroups, including patients aged >80 years, patients with severe stroke or mild stroke, patients with severe hypertension or elevated blood glucose, patients with previous stroke and concomitant diabetes, patients taking concomitant medications particularly anticoagulants and antiplatelets, and patients with stroke mimics.

The Group concluded that the current contraindications remain appropriate, but that there is some evidence indicating that the risk of rt-PA-induced ICH may be increased in the presence of severe leukoaraiosis. This degree of leukoaraiosis should be visible on a baseline CT scan of the brain and it would be appropriate for the SmPC to reflect this in the warnings and precautions. In addition, there is evidence to suggest that the risk is increased in patients taking dual anti-platelet therapy and this should also be reflected in the SmPC.

The Group noted that the MAH intends to submit a review of benefits and risks in patients aged over 80 years, to determine whether the contraindication in this population should be lifted. The review will include assessment of specific subgroups of elderly patients, in order to identify any groups of patients over 80 years for whom treatment with rt-PA is associated with a negative benefit:risk balance.

Medication error

The available data suggest that the main source of error is in the dosing and administering of rt-PA. This stems from the requirement for weight-based dosing and the inherent difficulties associated with weighing this population of patients. Where estimates of weight are provided, patients have been found to be the most accurate, followed by family/carers, and then healthcare professionals. In this regard, the Group considered that clinical guidance could be updated to provide advice for optimal but realistic weight estimation of stroke patients and that data on medication/dosing errors should be routinely recorded and reported in the Sentinel Stroke National Audit Program.

Risk minimisation measures (included as part of the marketing authorisation)

The EWG concluded that in general the conditions for use as specified in the SmPC for rt-PA in the indication of acute ischaemic stroke are appropriate, however the product information could be improved by:

- Updates to the dosing and administration section, including provision of a dosing table according to patient weight
- Update of the warnings and precautions/interactions sections to inform physicians about the deleterious synergistic effects of dual antiplatelet

therapy as the risks of rt-PA therapy may outweigh any potential benefits in those receiving aspirin and clopidogrel if there are any additional adverse prognostic features (e.g. severe stroke, old age)

- Update of the warnings and precautions section to inform physicians of an increased risk of sICH after rt-PA treatment in patients with leukoaraiosis or other established brain lesions at stroke onset

National tools to communicate risk to patients (as distinct from the marketing authorisation)

The EWG discussed the challenges associated with the communication of the balance of benefits and risks of rt-PA to individual patients and their families/carers at the time of the acute event, including the impact of the stroke symptoms themselves, the effect of the emotional stress associated with the situation and the time pressure under which the discussion and decisions have to be made. The Group was informed that Professor Gary Ford and colleagues had developed a computerised decision risk tool, which would be capable of providing individualised information on benefits and risks, and that work is ongoing to make this available within the NHS.

The EWG concluded that standardised information resources may be a beneficial resource and recommended that potential information outputs could include:

- Written information for use at the time of stroke: very concise and simple, pictorial/graphical in nature
- More extensive written information for patients/families to take away with them
- Explanatory notes/user guide for clinicians, to also include a weight based dosing table and advice on weight estimation of stroke patients
- Written information to proactively educate members of the general public particularly those at risk of stroke, including risk factors, signs and symptoms, seeking medical help and treatment options including thrombolysis

The EWG also discussed the possibility of the formation of a small subgroup to take forward the design, optimisation and methods of distribution of the proposed information resources.

3.1 Draft EWG recommendations to CHM

- On the basis of all the evidence presented the balance of benefits and risks of rt-PA in the treatment of acute ischaemic stroke is positive when used within the conditions of the marketing authorisation, up to 4.5 hours post-symptom onset.
- The Summary of Product Characteristics (SmPC) is considered to adequately describe the benefit-risk balance for rt-PA therapy according to: stroke severity; time to onset of treatment; age; concomitant use of anticoagulants and co-morbidities of high blood pressure and previous stroke with or without high blood glucose.
- In general, the current contraindications for rt-PA treatment in acute ischaemic stroke contained in the SmPC are considered acceptable and in line with current evidence, however the current contraindication in patients over 80 years should be re-evaluated in the light of new evidence.

- In general the conditions for use as specified in the SmPC for rt-PA in the indication of acute ischaemic stroke are appropriate, however the product information could be improved by:
 - Updates to the dosing and administration section, including provision of a dosing table according to patient weight
 - Update of the warnings and precautions/interactions sections to inform physicians about the increase in risk of sICH in patients taking dual antiplatelet therapy and in patients with leukoaraiosis or other established brain lesions at stroke onset
- Standardised, clear and simple information resources could be developed to support clinicians in helping patients'/families to make decisions about treatment based on a better understanding of the individualised benefits and risks of rt-PA. A small subgroup could be formed to take forward the proposals for the design and distribution of such materials.

4. Next steps: Communication of the outcome of the EWG/CHM

The conclusions and recommendations of the EWG will be considered by the CHM at their meeting in July. The communication of the final CHM outcome will need to be carefully considered. The options for communications include:

- Pro-active press release, to be placed on the MHRA website and provided on request to journalists or press conference.
- Provision of a Public Assessment Report (PAR) that includes the evidence base which underpins the conclusions of the EWG.
- Article in the Drug Safety Update bulletin.
- A short submission to a relevant publication e.g. The Lancet providing the outcome of the review.

Points for discussion for the EWG

- To consider the draft conclusions and recommendations to CHM
- To comment on the proposals for disseminating the outcome of the EWG and CHM discussions.