Prescribing Information (UK) – STROKE ONLY

ACTILYSE® (alteplase)

10mg, 20mg and 50mg powder and solvent for solution for injection and infusion. Actilyse vials contain alteplase (recombinant human tissue-type plasminogen activator, rt-PA) dry powder 10mg, 20mg and 50mg, supplied with water for injections. **Indication:** Fibrinolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible within 4.5 hours after onset of symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques. The treatment effect is time-dependent, therefore earlier treatment increases the probability of favourable outcome. **Dose and Administration**: Treatment must be started as early as possible within 4.5 hours of the onset of symptoms. Beyond 4.5 hours there is a negative benefit risk ratio associated with Actilyse administration and it should not be administered. Total dose 0.9mg/kg (maximum 90 mg): 10% by iv bolus, remainder by iv infusion over 60 minutes. Refer to Summary of Product Characteristics for dosing table. Avoid iv heparin or platelet aggregation inhibitors such as aspirin in the 24 hours after treatment with Actilyse due to an increased haemorrhagic risk. Paediatric population: There is limited experience with the use of Actilyse in children and adolescents. Actilyse is contraindicated for the treatment of acute ischaemic stroke in children and adolescents under 16 years of age. The dose for adolescents 16-17 years old is the same as for adults. **Contraindications:** Hypersensitivity to any constituent or gentamicin (a trace residue from the manufacturing process) and situations with a high risk of haemorrhage such as: significant bleeding disorder at present or within past 6 months; known haemorrhagic diathesis; effective oral anticoagulant treatment; manifest or recent severe or dangerous bleeding; known history of or suspected intracranial haemorrhage; suspected subarachnoid haemorrhage or condition after subarachnoid haemorrhage from aneurysm; history of CNS damage; within 10 days of traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel; 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 and active hepatitis; major surgery or significant trauma in past 3 months; symptom onset more than 4.5 hours or symptom onset unknown and potentially more than 4.5 hours ago; minor neurological deficit or symptoms rapidly improving before infusion start; severe stroke; seizure at onset of stroke; evidence of ICH on CT-scan; symptoms of subarachnoid haemorrhage even if CT-scan normal; heparin within previous 48 hours and elevated thromboplastin time; history of stroke and concomitant diabetes; prior stroke within last 3 months; platelet count <100,000/mm^3; systolic blood pressure >185 mm Hg or diastolic >110 mm Hg, or aggressive management necessary to reduce BP to these limits; blood glucose <50 mg/dl or >400 mg/dl (< 2.8mM or > 22.2mM); not indicated for patients under 16 years. **Warnings and precautions:** Situations where there is an increased risk of bleeding, including recent small traumas. The elderly are at increased risk of intracranial haemorrhage. The use of rigid catheters, intramuscular injections and non-essential handling of the patient should be avoided during treatment with Actilyse. Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care and in the use of thrombolytic treatments, with the facilities to monitor. Risk of intracranial haemorrhage is increased in this indication, particularly in patients with: high risk of haemorrhage; pre-treatment with aspirin; treatment should not be delayed; can be used in patients over 80 years on an individual benefit-risk basis; carefully consider both the general health and the neurological status. Monitor BP, give iv antihypertensive treatment if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg. Immune-mediated hypersensitivity reactions associated with the administration of Actilyse can be caused by the active substance alteplase, gentamicin (a trace residue from the manufacturing process), any of the excipients, or the stopper of the glass vial with Actilyse powder contains natural rubber (a derivative of latex). There is also a risk of hypersensitivity reactions mediated through a non-immunological mechanism. Angio-oedema represents the most common hypersensitivity reaction reported with Actilyse. This risk may be enhanced in the indication acute ischaemic stroke and/or by concomitant treatment with ACE inhibitors. Patients treated should be monitored for angio-oedema during and for up to 24h after infusion. If a severe hypersensitivity reaction (e.g. angio-oedema) occurs, the infusion should be discontinued and appropriate treatment, which may include intubation, should be promptly initiated. 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 ≤ 1.3 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal). Paediatric population: When Actilyse is considered for the treatment of acute ischaemic stroke in carefully selected adolescents ≥ 16 years of age the benefit should be weighed carefully against the risks on an individual basis and discussed with the patient and parent/guardian as appropriate. Adolescents ≥ 16 years of age should be treated according to the instruction in the label for the adult population after imaging by appropriate techniques to rule out stroke mimics and confirming arterial occlusion corresponding to the neurological deficit. **Interactions**: Coumarin derivatives, oral anticoagulants, platelet aggregation inhibitors, heparin, GPIIb/IIIa antagonists and other agents influencing coagulation increase haemorrhage risk. Concomitant treatment with ACE inhibitors may enhance the risk of a hypersensitivity reaction. **Fertility, pregnancy and lactation**: There is a limited amount of data from the use of Actilyse in pregnant women. Nonclinical studies performed in doses higher than human doses exhibited foetal immaturity and/or embryotoxicity, secondary to the known pharmacological activity of the drug. Alteplase is not considered to be teratogenic. 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 human milk. Clinical data on fertility are not available, nonclinical studies performed with alteplase showed no adverse effect on fertility. **Undesirable effects**: Very common (≥1/10): Intracerebral haemorrhage represents the major adverse reaction in acute ischaemic stroke – discontinue Actilyse if potentially dangerous haemorrhage occurs, all haemorrhages e.g. ICH and non-ICH, recurrent ischaemia/angina pectoris, hypotension and heart failure/pulmonary oedema. Common (≥1/100 to <1/10): Intracerebral haemorrhage (in the treatment of acute myocardial infarction and acute massive pulmonary embolism), pharyngeal haemorrhage, gastrointestinal haemorrhage, ecchymosis, urogenital haemorrhage, injection site haemorrhage, cardiogenic shock, cardiac arrest and reinfarction. Uncommon (≥1/1,000 to <1/100): pulmonary haemorrhage, epistaxis, ear haemorrhage, reperfusion arrhythmias, mitral regurgitation, pulmonary/other systemic/cerebral embolism, ventricular septal defect, blood pressure decreased. Rare (≥1/10,000 to <1/1,000): eye haemorrhage, pericardial haemorrhage, retroperitoneal bleeding, hypersensitivity reactions (e.g. rash, urticaria, bronchospasm, angio-oedema, hypotension, shock), embolism, nausea. Very rare (<1/10,000): Serious anaphylaxis, events related to the nervous system – often associated with ischaemic/haemorrhagic cerebrovascular events. Not known: Bleeding in parenchymatous organs, vomiting, body temperature increased, fat embolism, blood transfusions (necessary). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 1 x 50mg Actilyse plus transfer device £432.00; 1 x 20mg Actilyse plus transfer device £259.20; 1 x 10mg Actilyse £172.80. All packs also contain the appropriate quantity of water for injections. **Legal category** POM. **MA number:** PL 00015/0120. **Marketing Authorisation Holder**: Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, RG12 8YS. Prescribers should consult the Summary of Product Characteristics for full prescribing information. See SPC for use in acute MI and acute PE. **Prepared in June 2019.**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

Boehringer Ingelheim

Actilyse® alteplase

PC-UK-101784 July 2019