PART VI SUMMARY OF THE RMP

Active substance	Alteplase
Product concerned	Actilyse
Name of MAH or applicant	Boehringer Ingelheim International GmbH, Ingelheim, Germany
DLP for this module	31 Oct 2015
Version number of RMP when this module was last updated	8.5

PART VI.1 ELEMENTS FOR SUMMARY TABLES IN THE EPAR

PVI.Table 1 Summary table of the safety concerns

Important identified risks	Symptomatic intracerebral haemorrhage; especially for - the time window beyond 4.5 hours - inappropriately late administration within the proposed time window of 4.5 hours Hypersensitivity reactions Non-ICH bleedings
Important potential risks	Embryotoxicity
Missing information	Conditions/Risk factors increasing the bleeding risk Minor strokes Seizures before/at onset of stroke Children Elderly Pregnancy and Lactation

PVI.Table 2 Table of ongoing and planned studies in the post-authorisation pharmacovigilance development plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports[3]
Data extraction from SITS-ISTR registry	The main objectives are to monitor the impact of the lift of the age restriction (>80 years of age) on alteplase utilisation in EU MRP countries. Secondary aims are the continuous assessment of the efficacy and safety profile of this additionally treated elderly population (>80 years) within the SITS-ISTR registry in regard of the lift of age restriction.	Elderly	Ongoing	Data will be extracted on a 6 months basis until at least 500 patients have been recruited. Data will be presented in the upcoming EU PBRER in 2022. If safety concerns become evident, immediate notification to the authorities will be performed.

PVI.Table 3 Summary table of post-authorisation efficacy development plan

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status (planned/started)	Date for submission of interim or final reports
None				

PVI.Table 4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
SICH, especially for: - the time window beyond 4.5 hours - inappropriately late administration within the proposed time window of 4.5 hours	Appropriate labelling in SmPC sections 4.1 Therapeutic indications, 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions, 4.5 Interactions with other medicinal products and other forms of interactions, and 4.8 Undesirable effects. Prescription only medicine. Use restricted to physicians experienced in treatment of stroke and in neurovascular care.	None
Hypersensitivity reactions	Appropriate labelling in SmPC sections 4.3 Contraindications, 4.4 Special warnings and precautions, and 4.8 Undesirable effects. Prescription-only medicine. Only to be used by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor this treatment.	None
Non-ICH bleedings	Appropriate labelling in SmPC sections 4.3 Contraindications, 4.4 Special warnings and precautions, 4.5 Interactions with other medicinal products and other forms of interactions, and 4.8 Undesirable effects. Prescription only medicine. Only to be used by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor this treatment.	None
Important potential risks		
Embryotoxicity	Appropriate labelling in SmPC sections 4.6 Pregnancy and lactation, and 5.3 Preclinical safety data. Prescription-only medicine.	None

PVI.Table 4 (cont'd) Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
Conditions/Risk factors increasing the bleeding risk	Appropriate labelling in SmPC sections 4.1 Therapeutic indications, 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, and 4.8 Undesirable effects. Prescription only medicine. Only to be used by physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor this treatment.	None
Minor strokes	Appropriate labelling in SmPC sections 4.3 Contraindications, and 4.4 Special warnings and precautions. Prescription-only medicine. Use restricted to physicians experienced in treatment of stroke and in neurovascular care	None
Seizures before/at onset of stroke	Appropriate labelling in SmPC section 4.3 Contraindications. Prescription-only medicine. Use restricted to physicians experienced in treatment of stroke and in neurovascular care.	None
Children	Appropriate labelling in SmPC sections 4.2 Posology and method of administration, 4.3 Contraindications, and 4.4 Special warnings and precautions. Prescription-only medicine.	None
Elderly	Appropriate labelling in SmPC section 4.4 Special warnings and precautions. Prescription-only medicine. Use restricted to physicians experienced in treatment of stroke and in neurovascular care.	None
Pregnancy and Lactation	Appropriate labelling in SmPC section 4.6 Pregnancy and lactation. Prescription-only medicine.	None

PART VI.2 ELEMENTS FOR A PUBLIC SUMMARY

Part VI.2.1 Overview of disease epidemiology

Ischaemic strokes are caused by the occlusion of an artery of the brain by a blood clot. Among people older than 55 years, a first-ever ischaemic stroke occurs worldwide each year in 264-568 persons in 100 000 [R09-0469].

Stroke occurs more commonly with increasing age [R12-4505, R12-4537], especially between 60 and 80 years, but it may occur in younger or older persons [P05-06954]. More men than women experience a stroke [R12-4505].

The risk for stroke is higher in patients with diabetes, high blood sugar, high blood pressure, high blood lipids, irregular heartbeat, ischaemic heart disease, smoking habits [R98-1497], or using some oral contraceptives [R12-4490].

In Europe and the United States, 30-60 in 100 000 patients die of stroke; in other countries (e.g. Russia, China, and Africa), more patients (120-240 in 100 000) die of stroke [R12-4499]. Early death is more likely in patients with atrial fibrillation, ischaemic heart disease, diabetes, and ex-smokers [R09-0466].

Part VI.2.2 Summary of treatment benefits

Alteplase, the active substance of Actilyse®, dissolves blood clots and restores blood supply in occluded arteries (a process called thrombolysis). Thrombolysis with alteplase was the first and remains the only proven treatment approved for acute stroke caused by blood clots [P95-4908, P08-12177].

Administration of alteplase within 4.5 hours after beginning of stroke symptoms improves the patient´s outcome [P08-12177, P04-03314] and is recommended by guidelines for acute ischaemic stroke [P13-03861]. Alteplase significantly improved the clinical outcomes 3 months after stroke, as compared to patients who received placebo, in clinical studies on 291 and 333 patients who received treatment within 3 hours after stroke [P95-4908], and on 821 patients treated between 3 and 4.5 hours after stroke [P08-12177].

Two observational studies of the routine clinical practice [P07-00880, P08-11746] showed that alteplase was effective and generally well tolerated when administered within 4.5 hours (especially within 3 hours) after beginning of stroke symptoms.

Several clinical studies [P10-05924] indicated that the benefit of alteplase therapy over placebo increased, and the risk of death decreased, with early treatment (within 4.5 hours) after stroke. There was no significant benefit when treatment was started later than 4.5 hours after stroke.

Part VI.2.3 Unknowns relating to treatment benefits

In the main studies with alteplase, the majority of patients were White; only 2 studies included patients older than 80 years. There is no evidence to believe that the clinical efficacy of alteplase would be different in patients of different ethnicities or in very old patients.

Part VI.2.4 Summary of safety concerns

PVI.Table 5 Important identified risks

Risk	What is known	Preventability
Bleeding in the brain associated to neurological deterioration (SICH), especially for: - the time window beyond 4.5 hours - inappropriately late administration within the proposed time window of 4.5 hours	Bleeding in the brain (ICH), is a known risk of intravenous thrombolysis treatment. During SICH, worsening of the neurologic condition (including consciousness) occurs. SICH may be life-threatening or result in permanent disability. In general, ICH occurs 10 times more frequently in patients treated with thrombolytics than in those not treated [P06-03694]. SICH occurs less frequently than intracerebral haemorrhage of any type, i.e. with or without symptoms, in about 1 of 4 cases [P07-09401]. Among the main risk factors for SICH there are older age, severity of stroke, high blood glucose, high blood pressure, and a history of congestive heart failure. In patients treated with alteplase, use of alteplase itself and a longer time between stroke onset and treatment are further risk factors for SICH [P07-10602, P07-00880]. Symptomatic intracerebral haemorrhage occurs in up to one in ten patients treated with alteplase and is the major adverse reaction in the treatment of a stroke caused by a blood clot in an artery of the brain (acute ischaemic stroke). Nevertheless, the benefit of alteplase treatment remains higher than the overall risks as compared to placebo [P10-05924].	Each patient should be carefully evaluated and treatment benefits weighed against potential risks. Treatment must be started as soon as possible after beginning of symptoms. The overall clinical benefit is not favourable for alteplase when used more than 4.5 hours after start of symptoms. Therefore, such administration must be avoided as described in the indications, contraindications, special warnings and precautions for use, and interactions, in the SmPC.
Allergic reactions / Anaphylaxis (Hyper-sensitivity reactions)	Allergy (hypersensitivity) is a condition in which the body reacts with an exaggerated immune response to what is perceived as a foreign substance, for example to a drug. Serious allergic reactions include anaphylaxis, which requires hospitalisation. Allergic reactions (/anaphylaxis) associated with the administration of alteplase can be caused by allergy to the active substance itself, to gentamicin (a residue from the manufacturing process), or to any of the excipients. The stopper of the glass vial contains natural rubber (a derivative of latex), which might also cause allergic reactions. In patients treated with alteplase, allergic reactions occur in less than 1 in 1000 patients, and serious allergic reactions like anaphylaxis in less than 1 in 10 000 patients.	Patients with a known allergy (hypersensitivity) to the active substance alteplase or to its excipients must not receive Actilyse®, as described in the contraindications section of the SmPC.
Bleeding outside of the brain (Non-ICH) bleedings	Bleeding is an identified risk of all thrombolytic drugs, and may be either superficial (e.g. from punctures or damaged blood vessels) or internal (at any site or body cavity). Bleeding may occur very commonly, in more than 1 in 10 patients upon alteplase treatment for acute ischaemic stroke; major bleedings occur in less than 1 in 10 patients. In acute myocardial infarction, the concomitant use of heparin anticoagulation may contribute to bleeding.	Administration of alteplase must be avoided in patients at high risk of haemorrhage. The medical conditions that increase this risk are described in the contraindications, special warnings and precautions for use, and interactions in the SmPC.

PVI.Table 6 Important potential risks

Risk	What is known (incl. reason why it is considered a potential risk)
Toxic effects on the embryo (Embryotoxicity)	This potential risk is based on evidence from non-clinical studies of alteplase in rabbits, in which increased embryonal death and growth retardation were observed upon treatment with alteplase during pregnancy at doses that were three times higher than those used in the clinical therapy. However, in non-clinical studies with rats, no effects on embryonal and post-natal development or on fertility were observed even at much higher doses, up to 10 times higher than therapeutic doses.

PVI.Table 7 Missing information

Risk	What is known
Conditions / Risk factors increasing the bleeding risk	Some patients may be at high risk for bleeding when using thrombolytics because of certain illnesses or medical conditions. These prevented participation in clinical studies and are contraindications for the use of alteplase according to the SmPC. Therefore, there is limited experience on the use of Actilyse® in these patients. Medical conditions that lead to a high risk of bleeding are listed in the patient leaflet.
Very mild stroke symptoms (Minor stroke symptoms)	The use of alteplase in patients with very mild stroke symptoms is contraindicated, because in these patients the risks of bleeding might overweigh the treatment benefit. These patients were excluded from participation in clinical studies and are excluded from treatment with alteplase according to the approved contraindications. Therefore, there is limited experience on the use of Actilyse® in these patients.
Cramps (convulsions) before or at beginning of stroke (Seizures before/at onset of stroke)	Some patients thought to suffer from stroke may have also uncontrolled cramps of the body muscles, which are caused by an abnormal neuronal activity in the brain (seizures). Since the presence of convulsions makes a diagnosis of stroke difficult and increases the risk of bleeding, these patients were excluded from participation in clinical studies and are excluded from treatment with alteplase according to the approved contraindications. Therefore, there is limited experience on the use of Actilyse® in these patients.
Children	Actilyse® is not approved for treatment of acute stroke in children and adolescents (under 18 years). There are no data on use of alteplase in children from clinical trials; very few cases of unapproved use in children and very limited experience are available from the post-marketing experience.
Elderly	Elderly patients have a higher mortality rate and poorer functional outcomes than younger patients, which is consistent with the natural course of aging. Nevertheless, data from clinical trials and from observational studies show that treatment with alteplase in patients > 80 years improves stroke outcomes and does not increase bleeding rates. Treatment of the elderly (> 80 years) with alteplase should be initiated following careful assessment for other contraindications and also by carefully weighing the benefits against the risks on an individual basis.
Pregnancy and Lactation	There is very limited experience with the use of alteplase during pregnancy and lactation. Because of the toxicity to the embryo observed in some non-clinical studies with rabbits, the use of alteplase during pregnancy is not recommended. 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.

Part VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the PL. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post-authorisation development plan

PVI.Table 8 List of studies in post-authorisation development plan

Study/activity (incl. study number)	Objectives	Safety concerns/ efficacy issue addressed	Status	Planned submission date of (interim and) final results
Data extraction from SITS-ISTR registry	The main objectives are to monitor the impact of the lift of the age restriction (>80 years of age) on alteplase utilisation in EU MRP countries. Secondary aims are the continuous assessment of the efficacy and safety profile of this additionally treated elderly population (>80 years) within the SITS-ISTR registry in regard of the lift of age restriction.	Elderly	Ongoing	Data will be extracted on a 6 months basis until at least 500 patients have been recruited. Data will be presented in the upcoming EU PBRER in 2022. If safety concerns become evident, immediate notification to the authorities will be performed.

Part VI.2.7 Summary of changes to the RMP over time

PVI.Table 9 Major changes to the RMP over time

Version	Date	Safety concerns	Comment
7.0	24 Jun 2013	- The potential risk "embryotoxicity" was added - Missing information was added: conditions/risk factors increasing the bleeding risk; minor stroke symptoms; seizures before/at onset of stroke; children; elderly; pregnancy and lactation	The RMP was updated as requested in the assessment report for RMP version 6 (procedure DE/H/0015/001+004/IB/089)
7.1	27 Jan 2015	- Completed SITS-UTMOST study was included - Formal update of Module SVII, sub-sections in SVII.3.1 and 3.2 added	-
8.0	06 Apr 2017	- Children - Elderly	Extension of special population