Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for alteplase the scientific conclusions are as follows:

Based on the review of data from post-marketing surveillance and literature, the PRAC recommends an SmPC amendment of medicinal products containing alteplase, indicated for the thrombolytic treatment in acute myocardial infarction, acute massive pulmonary embolism with haemodynamic instability and of acute ischaemic stroke, for a better reflection of the risk of angio-oedema in sections 4.4, 4.5; moreover, in order to better reflect the risk of hypersensitivity reactions occurring with alteplase, sections 4.4, 4.5 and 4.8 of the SmPC of all alteplase containing products should be amended. No updates of the Package Leaflet are necessary since patient-specific information is not affected by the proposed changes to the SmPC.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for alteplase the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing alteplase is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing alteplase are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

For alteplase containing products authorised for the thrombolytic treatment in acute myocardial infarction, in acute massive pulmonary embolism with haemodynamic instability and of acute ischaemic stroke:

- Section 4.4

Hypersensitivity

~~No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systematic experience with re-administration of Actilyse. Anaphylactoid~~ **Immune-mediated hypersensitivity** 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~~.~~**, or** ~~The~~ **the** stopper of the glass vial with Actilyse powder **which** contains natural rubber (a derivative of latex)**.** ~~which may cause allergic reactions~~. **No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systematic experience with re-administration of Actilyse.**
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 (see section 4.5). Patients treated for any authorised indication should be monitored for angio-oedema during and for up to 24h after infusion.

If ~~an anaphylactoid reaction~~ **a severe hypersensitivity reaction (e.g. angio-oedema)** occurs, the infusion should be discontinued and appropriate treatment **promptly** initiated. **This may include intubation.**

- Section 4.5

Concomitant treatment with ACE inhibitors may enhance the risk of suffering ~~an anaphylactoid~~ **a hypersensitivity** reaction **(see section 4.4).**~~, as in the cases describing such reactions~~ ~~, as in the cases describing such reactions a relatively larger proportion of patients were receiving ACE inhibitors concomitantly.~~

- Section 4.8

Immune system disorders	
rare	hypersensitivity ~~/ 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

*~~Immune system disorders~~

~~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.~~ **See sections 4.4 and 4.5**

Summary of Product Characteristics

For alteplase containing products authorised for the thrombolytic treatment of occluded central venous access devices including those used for haemodialysis:

- Section 4.4

Hypersensitivity

Antibody formation in patients receiving one or more doses of alteplase for restoration of dysfunctional central venous access devices has not been studied. ~~Although physiologically relevant plasma concentrations are not reached, hypersensitivity might occur.~~ ~~Anaphylactoid~~ **Hypersensitivity** reactions associated with the administration of Actilyse Cathflo can be caused by ~~hypersensitivity to~~ the active substance alteplase, gentamicin (a trace residue from the manufacturing process)**,** ~~or to~~ any of the excipients~~.~~**,** **or** ~~The~~ **the** stopper of the glass vial with Actilyse Cathflo powder **which** contains natural rubber (a derivative of latex) ~~which may cause allergic reactions~~.

If ~~an anaphylactoid~~ **a severe hypersensitivity** reaction occurs, the instillation should be discontinued and appropriate treatment should be **promptly** initiated.

- Section 4.5

Concomitant treatment with ACE inhibitors may enhance the risk of suffering ~~an anaphylactoid~~ **a hypersensitivity** reaction~~, as in the cases describing such reactions a relatively larger proportion of patients were receiving ACE inhibitors concomitantly~~.

- Section 4.8

Immune system disorders	
rare	hypersensitivity ~~/ 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

*~~Immune system disorders~~

~~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.~~ **See sections 4.4 and 4.5**

In principle, all undesirable effects as found for the systemic application of Actilyse (using the 10, 20, 50 mg presentations of alteplase, please refer to respective SmPC) may also occur during treatment of occluded catheters in cases where Actilyse Cathflo (2 mg of alteplase) reaches the systemic circulation (e.g. haemorrhage, embolism, hypersensitivity/~~anaphylactoid~~ reactions, blood pressure decreased, nausea, vomiting, body temperature increased). However, pharmacokinetic data indicate that physiologically relevant plasma concentrations are not reached using this dosage.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 March 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	9 May 2018