Metalyse

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0072/G	This was an application for a group of variations. B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	04/03/2024	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	Updated certificate from an already approved manufacturer				
IA/0071	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	23/02/2024	n/a		
II/0070/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/12/2023	12/01/2024	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Metalyse-H-C-000306-II-0070-G'
II/0069/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	21/09/2023	n/a		

	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.e - Change in test procedure for AS or				

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.z - Change in control of the AS - Other variation B.I.b.z - Change in control of the AS - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the				

	manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
PSUSA/2888/ 202208	Periodic Safety Update EU Single assessment - tenecteplase	14/04/2023	n/a		PRAC Recommendation - maintenance
IB/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/01/2023	24/07/2023	SmPC, Annex II, Labelling and PL	
IB/0066/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.b.1 - Stability of FP - Extension of the shelf	14/09/2022	24/07/2023	SmPC	

	life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IAIN/0065	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	08/08/2022	24/07/2023	SmPC and PL	
II/0064/G	This was an application for a group of variations. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	02/09/2021	n/a		
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2021	06/01/2022	PL	
IA/0062	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	07/01/2021	n/a		

IAIN/0061/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	07/01/2021	06/01/2022	Annex II and PL	
IA/0060	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	21/08/2020	n/a		
IB/0059	B.I.a.z - Change in manufacture of the AS - Other variation	24/04/2020	n/a		
PSUSA/2888/ 201908	Periodic Safety Update EU Single assessment - tenecteplase	17/04/2020	n/a		PRAC Recommendation - maintenance
II/0057	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	25/10/2018	n/a		
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/07/2018	28/09/2018	PL	

IB/0055	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/10/2017	28/09/2018	SmPC, Annex II, Labelling and PL	
IA/0054	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	17/06/2016	n/a		
IB/0053/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	17/06/2016	n/a		
IB/0052	B.I.b.z - Change in control of the AS - Other variation	03/06/2016	n/a		
IB/0051	C.I.7.b - Deletion of - a strength	20/10/2015	21/10/2016	SmPC, Labelling and PL	
PSUSA/2888/201408	Periodic Safety Update EU Single assessment - tenecteplase	10/04/2015	n/a		PRAC Recommendation - maintenance
II/0049	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance	22/01/2015	n/a		

	which may have a significant impact on the medicinal product and is not related to a protocol				
IB/0048/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	27/10/2014	n/a		
II/0046	Update of sections 4.2, 4.3, 4.4, 4.6, 5.1 and 5.2 of the SmPC in order to include: a recommendation to administer Metalyse with caution in elderly patients (> 75 years); an amendment of the existing contraindication on concomitant use of Metalyse in patients on oral anticoagulants; a warning regarding transfer to a coronary intervention capable facility for adjunctive PCI and consequent clarification of existing warning on primary PCI; formatting/editorial changes in section "Fertility, Pregnancy and Lactation" and "Clinical Pharmacokinetics"; and results from the STREAM study. The MAH took also the opportunity to align the Product Information to the QRD template version 9. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	18/09/2015	SmPC and PL	In this variation the MAH proposed the update of the Metalyse product information to include a recommendation to administer Metalyse with caution in elderly patients (> 75 years); an amendment of the existing contraindication on concomitant use of Metalyse in patients on blood thinning drugs; a warning regarding need to transfer patients to a facility capable of ensuring appropriate treatment and diagnosis if they have received Metalyse as coronary intervention. The MAH included also results from the STREAM study which evaluated the efficacy and safety of a pharmaco-invasive strategy versus a strategy of standard primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction within 3 hours of onset of symptoms.

IG/0432	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/04/2014	n/a		
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/02/2014	20/02/2014	PL	
IB/0044/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall	13/03/2013	n/a		

	quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or				

	starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which				

	does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the				

	Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the				

	Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting				

	material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters				

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				

IB/0043	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/02/2013	20/02/2014	SmPC, Labelling and PL	
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		
IA/0041	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	13/04/2012	n/a		
II/0036	To revise the module 3 Drug Substance and Drug product sections. The changes include: -Change in analytical procedure for testing for the primary packaging material and the drug product. -Change in specifications and test procedures for active ingredient and finished product. Update of or change(s) to the pharmaceutical documentation	24/06/2010	06/07/2010		
II/0035	Amendment of Product Information adding Gentamicin (as impurity residue from the manufacturing process) in the relevant sections in the product SPC. In addition the MAH has taken the opportunity to update some sections using MedDRA terminology, SPC Guideline and QRD template. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/04/2010	04/06/2010	SmPC, Labelling and PL	Adding the information about gentamycin and exclusion of patients with a known hypersensitivity to the excipient gentamycin, a residue from the manufacturing process, from the therapy with Metalyse is one of the main changes to the Metalyse SPC and PL that were submitted with this type II variation. The wording proposal concerning gentamycin for SPC and PL is endorsed by the CHMP. The CHMP view is that the new wording will increase the safe use of Metalyse.

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				As to the adoption of several changes according to the SPC Guideline, the process of formal changing of former terms to MedDRA terms (Clinical Overview, 2.5.5.2.1) the criteria for redefinition of frequency categories for all labelled adverse reactions described in the Clinical Overview summarised different low level terms under one preferred term, e.g. conjunctival and ocularr haemorrhage under eye haemorrhage, described under section 2.5.5.2.3 are also endorsed. In addition to the changes resulting from the above mentioned measures, all adverse reactions have been shifted into a table, in accordance with the SPC Guideline. All proposed changes to the SPC are endorsed. The Package Leaflet (PL) has also been amended.
IB/0039	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	08/02/2010	n/a		
IB/0038	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	08/02/2010	n/a		
IB/0037	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	08/02/2010	n/a		
IA/0034	IA_09_Deletion of manufacturing site	05/03/2009	n/a	Annex II	
IB/0033	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	27/01/2009	n/a		
IB/0032	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	27/01/2009	n/a		

IA/0031	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	11/05/2007	n/a		
IA/0030	IA_37_a_Change in the specification of the finished product - tightening of specification limits	11/05/2007	n/a		
IA/0029	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	16/02/2007	n/a		
II/0028	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2007	05/03/2007	SmPC, Annex II, Labelling and PL	The MAH has updated sections 4.4 and 5.1 of the SPC in order to include information on the outcome and design of the ASSENT-4 PCI study. The outcome of ASSENT-4 PCI was unfavorable with regards to primary endpoint (death, cardiogenic shock or congestive heart failure) for the facilitated (+Tenecteplase) PCI treatment in comparison to standard PCI treatment. The following text was added to Section 4.4: "Primary Percutaneous Coronary Intervention If primary PCI is scheduled according to the current relevant treatment guidelines, Metalyse as administered in the ASSENT-4 PCI study (see section 5.1) should not be given." and to Section 5.5: The ASSENT-4 PCI study was designed to show if in 4000 patients with large myocardial infarctions pre-treatment with full dose tenecteplase and concomitant single bolus of up to 4,000 IU unfractionated heparin administered prior to primary Percutaneous Coronary Intervention (PCI) to be

					performed within 60 to 180 minutes leads to better outcomes than primary PCI alone. The trial was prematurely terminated with 1667 randomised patients due to a numerically higher mortality in the facilitated PCI group receiving tenecteplase. The occurrence of the primary endpoint, a composite of death or cardiogenic shock or congestive heart failure within 90 days, was significantly higher in the group receiving the exploratory regimen of tenecteplase followed by routine immediate PCI: 18.6% (151/810) compared to 13.4% (110/819) in the PCI only group, p=0.0045. This significant difference between the groups for the primary endpoint at 90 days was already present in-hospital and at 30 days. Numerically all of the components of the clinical composite endpoint were in favour of the PCI only regimen: death: 6.7% vs. 4.9% p=0.14; cardiogenic shock: 6.3% vs. 4.8% p=0.19; congestive heart failure: 12.0% vs. 9.2% p=0.06 respectively. The secondary endpoints re-infarction and repeat target vessel revascularisation were significantly increased in the
R/0027	Renewal of the marketing authorisation.	14/12/2005	13/02/2006	SmPC, Annex II, Labelling and PL	
II/0022	Quality changes	17/11/2005	25/11/2005		
II/0023	Change(s) to the test method(s) and/or specifications for the active substance	15/09/2005	23/09/2005		
IB/0025	IB_12_b_02_Change in spec. of active subst./agent	21/09/2005	n/a		

	in manuf. of active subst. - test parameter				
IB/0026	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	16/09/2005	n/a		
IA/0024	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	14/09/2005	n/a		
IB/0018	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	19/08/2005	n/a		
IB/0015	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	12/01/2005	n/a		
IB/0017	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec. IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	21/12/2004	n/a		
IB/0016	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec. IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	21/12/2004	n/a		
IB/0014	IA_13_a_Change in test proc. for active substance - minor change IB_12_a_Change in spec. of active subst./agent used	17/12/2004	n/a		

	in manuf. of active subst. - tightening				
IA/0013	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	17/11/2004	n/a		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/10/2004	n/a	PL	
II/0011	Change(s) to shelf-life or storage conditions	25/09/2003	27/01/2004	SmPC and PL	
II/0009	Update of Summary of Product Characteristics and Package Leaflet	25/09/2003	27/01/2004	SmPC and PL	
II/0007	Change(s) to container	25/04/2003	23/07/2003	SmPC, Labelling and PL	
I/0010	17_Change in specification of the medicinal product	02/07/2003	07/07/2003		
I/0008	01_Change in the name of a manufacturer of the medicinal product 11a_Change in the name of a manufacturer of the active substance	21/05/2003	25/06/2003	Annex II and PL	
I/0006	12_Minor change of manufacturing process of the active substance	22/05/2003	06/06/2003		
II/0004	Update of Summary of Product Characteristics and Package Leaflet	17/10/2002	24/01/2003	SmPC and PL	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/10/2002	27/11/2002	PL	

II/0003	New presentation(s)	30/05/2002	18/09/2002	SmPC, Labelling and PL	
II/0002	Quality changes Update of Summary of Product Characteristics and Package Leaflet	13/12/2001	02/04/2002	SmPC and Labelling	
II/0001	Quality changes	26/07/2001	15/10/2001		