EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Rapilysin

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
IG/1612	A.1 - Administrative change - Change in the name and/or address of the MAH	31/05/2023		SmPC, Labelling and PL	
IB/0074/G	This was an application for a group of variations.	17/02/2022	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).

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	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/01/2022		PL	
PSUSA/2623/202011	Periodic Safety Update EU Single assessment - reteplase	08/07/2021	n/a		PRAC Recommendation - maintenance
IA/0071	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	15/05/2019	n/a		
IB/0070	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/12/2018	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/08/2018		Labelling and PL	
PSUSA/2623/201711	Periodic Safety Update EU Single assessment - reteplase	12/07/2018	n/a		PRAC Recommendation - maintenance
IA/0066/G	This was an application for a group of variations.	11/04/2018	n/a		

	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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)				
IB/0068	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	06/04/2018	n/a		
IB/0067/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a	06/04/2018	n/a		

	starting material/reagent/intermediate for AS - Other variation				
N/0065	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/04/2018		PL	
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/08/2017		Labelling and PL	
II/0062	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	08/12/2016	n/a		
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/2016	06/07/2016	PL	
II/0056/G	This was an application for a group of variations. B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method 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.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling	04/02/2016	06/07/2016	Annex II and PL	

	down to 10-fold B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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 B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished				

	product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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)				
II/0058	Update of section 4.8 of the SmPC, upon request by PRAC following the assessment of a PSUR for Rapilysin (EMEA/H/C/PSUSA/00002623/201411), to add the ADR fat embolism. The Package Leaflet has been updated accordingly. Further, SmPC section 4.8 has been reformatted into a tabular format. In addition, the MAH took the opportunity to implement	17/12/2015	06/07/2016	SmPC, Annex II, Labelling and PL	Fat embolism has been added in SmPC section 4.8 under the SOC Injury, poisoning and procedural complications with the frequency not known (cannot be estimated from the available data). The corresponding section in the Package Leaflet has been updated as well.

	minor editorial changes, to update the contact details of the local representatives in NL, BE, LU and ES in the Package Leaflet, and to make minor updates in the SmPC, Annex II and the labelling in line with the latest QRD template (version 9.1, 06/2015). C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
IAIN/0060	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	10/12/2015	n/a		
IB/0059	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	10/12/2015	n/a		
II/0055/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [...] used in the manufacture of a biological/immunological product B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	19/11/2015	n/a		

	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS 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.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 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 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 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 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 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 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				

	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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0051/G	This was an application for a group of variations. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished	17/09/2015	06/07/2016	SmPC	

	product formulation - Change that does not affect the product information				
IAIN/0057	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	11/08/2015	n/a		
IB/0053/G	This was an application for a group of variations. 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 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.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	03/08/2015	n/a		

	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits				
IA/0054/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites	28/07/2015	06/07/2016	Annex II	
IAIN/0052/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 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.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product	24/07/2015	n/a		

IB/0050	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/07/2015	06/07/2016	SmPC, Labelling and PL	
PSUSA/2623/ 201411	Periodic Safety Update EU Single assessment - reteplase	09/07/2015	n/a		PRAC Recommendation - maintenance
IB/0048	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	05/03/2015	n/a		
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/08/2014	06/07/2016	PL	
IB/0045	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/07/2014	n/a		
IA/0046/G	This was an application for a group of variations. 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.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	13/06/2014	n/a		

IA/0044	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	18/03/2014	n/a		
IB/0043	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/03/2014	n/a		
IB/0041	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	30/07/2013	n/a		
IB/0042	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	18/07/2013	n/a		
IB/0040/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/01/2013	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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				
II/0037/G	This was an application for a group of variations. Transfer of the active substance manufacturer site and additional minor changes needed to be implemented as a consequence of the site transfer. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/06/2012	n/a		

	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.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.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.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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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				
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/05/2012	06/07/2016	PL	
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/03/2012	06/07/2016	PL	
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/05/2010	n/a	PL	
II/0035	Change in the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	23/07/2009	12/08/2009		
IA/0033	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	18/07/2008	n/a	Annex II and PL	
IA/0034	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	15/07/2008	n/a		
T/0032	Transfer of the marketing authorisation holder to Actavis Group PTC ehf.	21/05/2008	20/06/2008	SmPC, Labelling and	

	Transfer of Marketing Authorisation			PL	
II/0031	Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	14/06/2007	SmPC and PL	The MAH applied for a type II variation to change the section 6.6 of the SPC and the section 3 of the PIL to revise the instructions for the safe use and handling of the medicinal product in order to address an incompatibility of the glass syringe of Rapilysin and the medical needle-free connector device reported in hospitals in the UK and Ireland.
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/02/2007	n/a	PL	
R/0029	Renewal of the marketing authorisation.	01/06/2006	10/08/2006	SmPC, Annex II, Labelling and PL	The renewal was granted with unlimited validity and PSURs will be submitted at 3-yearly intervals.
IA/0028	IA_01_Change in the name and/or address of the marketing authorisation holder	09/12/2005	n/a	SmPC, Labelling and PL	
II/0027	Update of Summary of Product Characteristics (4.2), Labelling and Package Leaflet Update of Summary of Product Characteristics, Labelling and Package Leaflet	15/09/2005	27/10/2005	SmPC, Labelling and PL	Compliance with latest QRD template
II/0026	Change(s) to the test method(s) and/or specifications for the active substance	21/04/2005	27/04/2005		
II/0024	Quality changes	16/09/2004	23/09/2004		

N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/07/2004	n/a	PL	
II/0023	Change(s) to the manufacturing process for the active substance	23/06/2004	25/06/2004		
II/0021	Update of Summary of Product Characteristics and Package Leaflet	22/05/2003	07/08/2003	SmPC and PL	
I/0022	MAH applies for the extension of the shelf-life for the intermediates. 12a_Change in specification of starting material/intermediate used in manuf. of the active substance	24/06/2003	26/06/2003		
I/0019	12_Minor change of manufacturing process of the active substance	25/04/2003	02/05/2003		
I/0020	24_Change in test procedure of active substance	18/03/2003	26/03/2003		
I/0018	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	18/03/2003	26/03/2003		
II/0017	Update of or change(s) to the pharmaceutical documentation	13/12/2001	27/03/2002	SmPC	
R/0016	Renewal of the marketing authorisation.	26/07/2001	09/11/2001	SmPC, Annex II, Labelling and PL	

II/0014	Quality changes	26/04/2001	11/05/2001		
I/0015	24_Change in test procedure of active substance	26/04/2001	n/a		
II/0012	Update of Summary of Product Characteristics and Package Leaflet	16/11/2000	20/03/2001	SmPC and PL	
I/0013	12_Minor change of manufacturing process of the active substance	01/03/2001	13/03/2001		
II/0011	New safety warning	16/02/2000	29/05/2000	SmPC and PL	
I/0010	01_Change following modification(s) of the manufacturing authorisation(s)	03/02/1999	08/04/1999	Annex II, Labelling and PL	
T/0009	Transfer of Marketing Authorisation	03/02/1999	19/03/1999	SmPC, Labelling and PL	
I/0008	14_Change in specifications of active substance	16/09/1998	08/10/1998		
II/0007	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/06/1998	05/10/1998	SmPC, Labelling and PL	
I/0006	20_Extension of shelf-life as foreseen at time of authorisation	10/02/1998	15/04/1998	SmPC	
II/0004	Change in formulation	19/11/1997	18/03/1998	SmPC, Labelling and PL	

II/0005	Change(s) to the manufacturing process for the active substance	25/02/1998	n/a		
I/0002	15_Minor changes in manufacture of the medicinal product	24/09/1997	n/a		
II/0001	Change(s) to shelf-life or storage conditions	23/07/1997	n/a		
I/0003	15_Minor changes in manufacture of the medicinal product	23/07/1997	n/a		