



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Cinryze

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
II/0104	Update of sections 4.6, 5.1 and 5.3 of the SmPC based on final results from the Icatibant Outcome Survey (IOS), listed as an imposed PASS in the Annex II. This is a prospective, observational disease registry. The Package Leaflet is updated accordingly. The RMP version 11.2 has also been submitted. In	08/05/2025		SmPC, Annex II, Labelling and PL	SmPC new text Pregnancy Human C1-esterase inhibitor is a physiological component of human plasma. Therefore, no adverse effects on fertility, pre- and post-natal development are expected in humans. Animal-reproductive studies show no maternal or

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).



	addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the product information in line with the latest QRD template version 10.4 and to update Annex II of the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				embryofoetal effects in rats at dose levels up to 28 times the recommended human dose (1 000 IU) based on an average adult body weight of 70 kg. Data on a limited number of exposed pregnancies are available from clinical studies and from post-marketing experience (including data from two observational studies) and indicate no adverse effects of human C1-esterase inhibitor on pregnancy or on the health of the foetus/newborn child (see section 5.1). Cinryze should be given to pregnant women only if clearly indicated. For more information, please refer to the Summary of Product Characteristics.
IB/0103	B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR	10/09/2024	n/a		
IA/0102/G	This was an application for a group of variations. B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	16/08/2024	n/a		

	procedure				
IAIN/0101	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	14/05/2024	n/a		
IB/0100	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/05/2024		SmPC and PL	
PSUSA/10104 /202306	Periodic Safety Update EU Single assessment - human C1-esterase inhibitor	08/02/2024	n/a		PRAC Recommendation - maintenance
IB/0099	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/10/2023	n/a		
IB/0097/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/07/2023	n/a		
IAIN/0096	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	15/05/2023	n/a		

IAIN/0095	A.3 - Administrative change - Change in name of the AS or of an excipient	06/10/2022	09/10/2023	SmPC, Labelling and PL	
IAIN/0094	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	13/07/2022	n/a		
T/0093	Transfer of Marketing Authorisation	15/03/2022	17/05/2022	SmPC, Labelling and PL	
PSUSA/10104 /202106	Periodic Safety Update EU Single assessment - human C1-esterase inhibitor	10/02/2022	n/a		PRAC Recommendation - maintenance
IAIN/0092/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.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.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)	28/01/2022	17/05/2022	Annex II and PL	

	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.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) 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) 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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites				
IB/0091	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	06/01/2022	n/a		

	or addition) for the AS or a starting material/intermediate				
II/0089	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	02/12/2021	n/a		
IAIN/0088	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	12/07/2021	n/a		
IAIN/0087/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/05/2021	n/a		
IAIN/0086	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	23/02/2021	n/a		

II/0082/G	This was an application for a group of variations. B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS 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 bio/immunol method 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.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	18/02/2021	24/01/2022	Annex II	
IAIN/0085	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	01/02/2021	24/01/2022	Annex II and PL	
IB/0081	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/10/2020	24/01/2022	SmPC, Annex II, Labelling and PL	
IA/0083	A.7 - Administrative change - Deletion of manufacturing sites	08/10/2020	n/a		

IAIN/0080	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	25/09/2020	n/a		
IAIN/0079	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	24/07/2020	n/a		
IB/0078	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	22/06/2020	n/a		
IAIN/0077	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	20/05/2020	n/a		
IAIN/0076	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	23/03/2020	31/07/2020	Annex II and PL	
PSUSA/10104 /201906	Periodic Safety Update EU Single assessment - human C1-esterase inhibitor	16/01/2020	n/a		PRAC Recommendation - maintenance

IB/0075	B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP	20/12/2019	n/a		
IAIN/0074	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	03/12/2019	n/a		
II/0071/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.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.2.z - Changes in the manufacturing process of the AS - Other variation 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.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/11/2019	n/a		

	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes 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 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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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 product formulation - Change that does not affect the product information				
IAIN/0072/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	08/07/2019	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
II/0069	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/06/2019	31/07/2020	SmPC and PL	
IAIN/0070/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/03/2019	n/a		

IB/0067/G	This was an application for a group of variations. 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.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 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.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.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)	20/02/2019	n/a		
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IB/0068	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	30/01/2019	n/a		
II/0064	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	17/01/2019	n/a		
IA/0066	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	24/10/2018	n/a		
IAIN/0063	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	02/05/2018	n/a		
IAIN/0062	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	19/04/2018	n/a		
IA/0061	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	20/03/2018	n/a		

IAIN/0060	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	20/03/2018	27/08/2018	Annex II and PL	
IAIN/0059	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	16/03/2018	n/a		
II/0058/G	This was an application for a group of variations. 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.2.z - Changes in the manufacturing process of the AS - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/03/2018	n/a		
PSUSA/10104 /201706	Periodic Safety Update EU Single assessment - human C1-esterase inhibitor	11/01/2018	n/a		PRAC Recommendation - maintenance
IB/0057/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS -	09/11/2017	n/a		

	Tightening of in-process limits 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				
IB/0056	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	27/10/2017	n/a		
II/0048	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2017	27/08/2018	SmPC, Labelling and PL	The term Unit (U) is replaced by International Unit (IU) for the product potency throughout the product information. Historically assigned potency values were relative to an in-house reference standard whereby 1 Unit (U) is equal to the mean quantity of C1 inhibitor present in 1 ml of normal human plasma. An international reference standard (IU) has now been implemented where IU is also defined as the amount of C1 inhibitor present in 1 ml of normal human plasma.
IAIN/0054	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	23/06/2017	n/a		
IA/0053/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	01/06/2017	n/a		

IB/0052	B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP	26/05/2017	n/a		
IA/0051	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	15/05/2017	n/a		
IB/0049/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation	04/05/2017	n/a		
IAIN/0050/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes	24/03/2017	n/a		

	do not affect the properties of the FP				
II/0045	Extension of Indication in children with hereditary angioedema (HAE) to include the treatment and pre-procedure prevention of angioedema attacks from 2 years and the routine prevention of angioedema attacks from 6 years; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC are updated. The key messages of educational materials in the Annex II, the Package Leaflet and the Labelling are updated in accordance. In addition, an update of regional information in module 3.2.R due to the proposed dose recommendation for children is submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/12/2016	26/01/2017	SmPC, Labelling and PL	Please refer to the CHMP AR.
PSUSA/10104/201606	Periodic Safety Update EU Single assessment - human C1-esterase inhibitor	12/01/2017	n/a		PRAC Recommendation - maintenance
IA/0047/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.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	20/10/2016	26/01/2017	Annex II	

	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 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) 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) 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				
IA/0044	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	21/06/2016	n/a		
IAIN/0043	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	01/06/2016	n/a		

R/0040	Renewal of the marketing authorisation.	01/04/2016	26/05/2016	SmPC, Annex II, Labelling and PL	
IAIN/0042	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	29/04/2016	n/a		
PSUSA/10104/201506	Periodic Safety Update EU Single assessment - human C1-esterase inhibitor	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0039	Early discontinuation of the Cinryze Registry Study 0624-401 and replacement by the Icatibant Outcome Survey (IOS), Disease Registry for compliance with an Annex II.D condition. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	17/12/2015	n/a		
IG/0603/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	03/12/2015	26/05/2016	SmPC, Annex II, Labelling and PL	

IB/0035	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	06/11/2015	n/a		
IG/0621	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	16/10/2015	n/a		
IAIN/0038	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/10/2015	n/a		
IB/0032/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.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	27/07/2015	26/05/2016	Annex II	
IA/0034	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/07/2015	n/a		
IA/0033	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/07/2015	n/a		

IB/0030/G	This was an application for a group of variations. B.I.b.1.a - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits for medicinal products subject to OCABR 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.d.2.a - Change in test procedure for the finished product - 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.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	30/04/2015	n/a		
IAIN/0031	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	09/04/2015	n/a		
IAIN/0029	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) -	16/02/2015	n/a		

	Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IB/0028/G	This was an application for a group of variations. B.II.e.1.b.z - Change in immediate packaging of the finished product - Type of container - Other variation 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.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.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	14/01/2015	n/a		
PSUV/0027	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
PSUV/0023	Periodic Safety Update	24/07/2014	30/09/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0023.
IAIN/0025	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	02/07/2014	n/a		
IAIN/0024	B.V.a.1.d - PMF - Inclusion of a new, updated or	11/06/2014	n/a		

	amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IB/0022	B.II.b.z - Change in manufacture of the Finished Product - Other variation	01/06/2014	n/a		
IAIN/0021	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	11/04/2014	n/a		
II/0017	Submission of the final study report of study 0624-203: "an open-label single-dose study to evaluate the response and pharmacokinetics / pharmacodynamics of different doses of CINRYZE for treatment of acute angioedema attacks in children less than 12 years of age with hereditary angioedema" in order to fulfil the requirement of article 46 of the paediatric regulation. No change to the product information was required. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/03/2014	n/a		Please refer to the scientific discussion Cinryze EMEA/H/C/001207/II/0017 for further information.
IB/0019	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g.	13/03/2014	n/a		

	duplication of line)				
IB/0018/G	This was an application for a group of variations. B.II.e.z - Change in container closure system of the Finished Product - Other variation B.IV.1.b - Change of a measuring or administration device - Deletion of a device	20/02/2014	30/09/2014	SmPC, Labelling and PL	
IAIN/0020/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) in the safety database and/or major contractual arrangements for the fulfilment of PhV obligations, and/or change of the site undergoing PhV activities C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the PhV system	17/02/2014	n/a		
PSUV/0016	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0014	Changes to Drug product specification to fulfill Annex II condition 002. Changes in the due date for conditions 003 and 004. B.II.d.z - Change in control of the Finished Product -	19/09/2013	30/09/2014	SmPC, Annex II and PL	

	Other variation				
IAIN/0015	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	18/07/2013	n/a		
IAIN/0013/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	19/03/2013	n/a		
IAIN/0012/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes	06/03/2013	n/a		

	do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
II/0011	B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	15/11/2012	n/a		
IB/0005	B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	09/11/2012	n/a		
II/0003	To calibrate an in house concentrate standard against WHO 1 international standard for c1-inhibitor. This variation is to fulfil Annex II condition 001. B.II.z - Quality change - Finished product - Other variation	20/09/2012	25/10/2012	Annex II	
IAIN/0010	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	14/09/2012	25/10/2012	Annex II and PL	
IAIN/0009/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the	22/08/2012	n/a		

	major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IA/0008	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	17/08/2012	n/a		
IB/0007	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	17/08/2012	25/10/2012	SmPC, Labelling and PL	
IAIN/0004/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	12/07/2012	n/a		

II/0001	Amendment (timetable extension) of the conditions of the Marketing Authorisation B.II.z - Quality change - Finished product - Other variation	19/04/2012	22/05/2012	Annex II	
IB/0002/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale A.6 - Administrative change - Change in ATC Code/ATC Vet Code	14/04/2012	22/05/2012	SmPC, Labelling and PL	