EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Soliris

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
IA/0129	A.7 - Administrative change - Deletion of manufacturing sites	14/08/2023		Annex II and PL	
II/0126	Extension of indication to include treatment of paediatric patients with refractory generalised myasthenia gravis (gMG) for Soliris, based on	22/06/2023	24/07/2023	SmPC, Labelling and	Please refer to Scientific Discussion 'Soliris-H-C-000791-II-0126'

[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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	interim results from study ECU-MG-303; this is an open-label, multicenter, phase 3 study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of intravenous (IV) eculizumab in paediatric patients aged 6 to less than 18 years with acetylcholine receptor-antibody (AChR-Ab) positive (+) refractory gMG. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.3 of the RMP has been agreed. In addition, the MAH took the opportunity to update section 4.8 of the SmPC in order to update the frequency of the list of adverse drug reactions (ADRs) based on cumulative safety data and to introduce minor editorial changes to the PI. In addition, in line with the new WHO level alteration, the Marketing authorisation holder (MAH) took the opportunity to update the ATC code in the SmPC section 5.1. The list of local representatives in the Package Leaflet has been updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			PL	
IAIN/0127/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	18/04/2023	24/07/2023	Annex II and PL	

	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.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release				
IB/0125	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	28/11/2022	n/a		
IB/0124	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/11/2022	24/07/2023	SmPC, Annex II and PL	
IB/0123	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	08/11/2022	n/a		
II/0122	Submission of the final report from study ECU-NMO-302, a phase III, open-label, extension trial of ECU-NMO-301 to evaluate the safety and efficacy of eculizumab in subjects with neuromyelitis optica spectrum disorder (NMOSD) following procedure II/0105. Section 5.1 of the SmPC is updated to include the results of the final analysis of Study ECU-NMO-302. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	01/09/2022	24/07/2023	SmPC	SmPC new text The final analysis of Study ECU-NMO-302 demonstrates a significant and clinically meaningful reduction in On-trial ARR (as determined by the Treating Physician) on eculizumab treatment, based on the median (min, max) change (-1.825 [-6.38, 1.02], p<0.0001) from historical ARR (24 months prior to screening in Study ECU-NMO-301). In Study ECU-NMO-302, physicians had the option to adjust background immunosuppressant therapies. In this

	of studies to the competent authority				setting, the most common change in immunosuppressant therapy was decreased immunosuppressant therapy dose, which occurred in 21.0% of patients. Further, 15.1% of patients stopped an existing IST. For more information, please refer to the Summary of Product Characteristics.
PSUSA/1198/ 202110	Periodic Safety Update EU Single assessment - eculizumab	10/06/2022	n/a		PRAC Recommendation - maintenance
II/0121	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	22/04/2022	n/a		
II/0118/G	This was an application for a group of variations. 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 B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	03/02/2022	n/a		
IB/0119/G	This was an application for a group of variations. B.I.e.3 - Deletion of an approved change	06/01/2022	n/a		

	management protocol related to the AS B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product				
IB/0117/G	This was an application for a group of variations. 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.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 A.7 - Administrative change - Deletion of manufacturing sites	11/11/2021	n/a		
IA/0116	A.7 - Administrative change - Deletion of manufacturing sites	08/03/2021	18/03/2022	Annex II	
II/0115/G	This was an application for a group of variations. B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal 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	21/01/2021	19/02/2021	Annex II	

	biological/immunological product				
IAIN/0114	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	31/08/2020	n/a		
II/0113	Section 4.2 of the SmPC has been updated to include home-infusion as an alternative infusion setting for Soliris for all the approved indications. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2020	19/02/2021	SmPC	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No' Section 4.2 of the SmPC has been updated to include home-infusion as an alternative infusion setting for Soliris for all the approved indications.
II/0112	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	28/05/2020	n/a		
PSUSA/1198/201910	Periodic Safety Update EU Single assessment - eculizumab	14/05/2020	n/a		PRAC Recommendation - maintenance
II/0111	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/02/2020	19/02/2021	SmPC, Annex II and PL	
II/0107	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/12/2019	n/a		
IB/0109	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	12/09/2019	n/a		

II/0105	Extension of Indication to include treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and Annex II of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP was updated to version 19.3. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2019	26/08/2019	SmPC, Annex II and PL	Please refer to the scientific discussion Soliris-H-C-791-II-0105 for further information
IA/0108/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/08/2019	n/a		
IAIN/0106	A.1 - Administrative change - Change in the name and/or address of the MAH	25/07/2019	26/08/2019	SmPC, Labelling and PL	
II/0104/G	This was an application for a group of variations. 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	14/03/2019	n/a		

	method at the site is a biol/immunol method B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.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.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0103	To update SmPC section 4.4 describing reports of serious infections with Neisseria species (other than Neisseria meningitidis), including disseminated gonococcal infections, SmPC section 4.5 describing the theoretical potential for drug-drug interaction between eculizumab and intravenous human immunoglobulin (IVIg), and SmPC section 4.8, clarifying sepsis as the most common presentation of Neisseria meningococcal infections. The annex II and	20/09/2018	22/11/2018	SmPC, Annex II, Labelling and PL	As a result of this variation, the product information are updated with regards to: • SmPC sections 4.4 and 4.8, Annex II and PL sections 2 and 4: updated information on serious infection with Neisseria species (other than Neisseria meningitidis), including disseminated gonococcal infections • SmPC section 4.5: information on potential for drug-drug interaction between eculizumab and intravenous

	the package leaflet are updated accordingly. The MAH took the opportunity to align the Product information with the QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				human immunoglobulin (IVIg) • SmPC section 4.8: clarification on sepsis as the most common presentation of Neisseria meningococcal infections
II/0102	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/06/2018	n/a		
PSUSA/1198/ 201710	Periodic Safety Update EU Single assessment - eculizumab	12/04/2018	n/a		PRAC Recommendation - maintenance
II/0098	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	14/12/2017	22/11/2018	SmPC, Annex II, Labelling and PL	
II/0100	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	14/09/2017	n/a		
II/0090	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/06/2017	14/08/2017	SmPC, Annex II and PL	

IB/0099	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/07/2017	n/a		
IB/0097	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/06/2017	n/a		
II/0093	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	18/05/2017	n/a		
PSUSA/1198/ 201610	Periodic Safety Update EU Single assessment - eculizumab	05/05/2017	n/a		PRAC Recommendation - maintenance
IAIN/0095	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	18/04/2017	14/08/2017	Annex II and PL	
IB/0094/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion	05/04/2017	n/a		

	of a non-significant in-process test 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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0092	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	04/04/2017	n/a		
II/0086/G	This was an application for a group of variations. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	14/08/2017	SmPC, Annex II and PL	
II/0089	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	15/12/2016	n/a		

II/0088/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.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	15/12/2016	n/a		
IB/0087	B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation	22/07/2016	n/a		
IAIN/0084/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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	09/06/2016	19/09/2016	Annex II and PL	
IA/0085	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	26/05/2016	n/a		

	(excluding manufacturer for batch release)				
PSUSA/1198/ 201510	Periodic Safety Update EU Single assessment - eculizumab	14/04/2016	n/a		PRAC Recommendation - maintenance
IB/0083	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/03/2016	n/a		
IB/0082	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	01/03/2016	n/a		
II/0081/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.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	25/02/2016	19/09/2016	Annex II	
IB/0079/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of	08/01/2016	n/a		

	the AS - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
II/0077	Update of sections 4.3 and 4.4 of the SmPC to add the serogroup B vaccine in addition to the serogroups A, C, W135 and Y, to extend the possibility of urgent use of Soliris under prophylactic antibiotic treatment to PNH patients and to remove reference to tetravalent or conjugated vaccines. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 9.1 and to remove the list of local representatives. The updated RMP v.12.2 was agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	19/09/2016	SmPC, Annex II, Labelling and PL	
IB/0078	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/07/2015	20/07/2015		
IA/0076	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	29/05/2015	n/a		

PSUSA/1198/201410	Periodic Safety Update EU Single assessment - eculizumab	10/04/2015	n/a		PRAC Recommendation - maintenance
IA/0075/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.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.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.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.c.1.z - Change in immediate packaging of the AS - Other variation B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the	01/04/2015	n/a		

	dossier) - Deletion of a supplier				
II/0066	Extension of Indication to include paroxysmal nocturnal haemoglobinuria (PNH) where evidence of clinical benefit is demonstrated in patients with haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to correct some typographical errors in the product information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/02/2015	30/03/2015	SmPC and PL	Please refer to the scientific discussion Soliris-H-C-791-II-66.
II/0071/G	This was an application for a group of variations. Grouped application including three type II variations: Update of section 5.1 of the SmPC with clinical information for the paediatric and adult populations based on the final CSR for Study C10-003. Update of section 5.1 of the SmPC with clinical information for the paediatric and adult populations based on the final CSR for Study C10-004. Update of section 4.4 of the SmPC with further information regarding 'treatment discontinuation for aHUS' based on the interim report for the ongoing long-term study C11-003 (for patients included in	26/02/2015	30/03/2015	SmPC and PL	Treatment Discontinuation for aHUS: Thrombotic microangiopathy (TMA) complications have been observed as early as 4 weeks and up to 127 weeks following discontinuation of Soliris treatment in some patients. Discontinuation of treatment should only be considered if medically justified. In aHUS clinical studies, 61 patients (21 paediatric patients) discontinued Soliris treatment with a median follow-up period of 24 weeks. Fifteen severe thrombotic microangiopathy (TMA) complications in 12 patients were observed following treatment discontinuation, and 2 severe TMA complications occurred in an additional 2 patients that received a reduced dosing regimen of Soliris outside of the approved dosing regimen. Severe TMA complications

	the five completed clinical studies C08-002 A/B, C08-003 A/B, C09-001r, C10-003 and C10-004). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				occurred in patients regardless of whether they had an identified genetic mutation, high risk polymorphism or auto-antibody. Additional serious medical complications occurred in these patients including severe worsening of kidney function, disease-related hospitalization and progression to end stage renal disease requiring dialysis. Despite Soliris re-initiation following discontinuation, progression to end stage renal disease occurred in one patient. If aHUS patients discontinue treatment with Soliris, they should be monitored closely for signs and symptoms of severe thrombotic microangiopathy complications. Monitoring may be insufficient to predict or prevent severe thrombotic microangiopathy complications in patients with aHUS after discontinuation of Soliris. Adult population: Longer term treatment with Soliris (median 52 weeks ranging from 15 to 126 weeks) was associated with an increased rate of clinically meaningful improvements in adult patients with aHUS. When Soliris treatment was continued for more than 26 weeks, three additional patients (63% of patients in total) achieved Complete TMA response and four additional patients (98% of patients in total) achieved hematologic normalization. At the last evaluation, 25 of 41 patients (61%) achieved eGFR improvement of ≥ 15 mL/min/1.73 m2 from baseline. Paediatric population: Longer term treatment with Soliris (median 55 weeks ranging from 1day to 107 weeks) was associated with an increased rate of clinically meaningful improvements in

					pediatric and adolescent patients with aHUS. When Soliris treatment was continued for more than 26 weeks, one additional patient (68% of patients in total) achieved Complete TMA Response and two additional patients (91% of patients in total) achieved hematologic normalization. At the last evaluation, 19 of 22 patients (86%) achieved eGFR improvement of ≥ 15 mL/min/1.73 m2 from baseline. No patient required new dialysis with Soliris.
IA/0074	A.7 - Administrative change - Deletion of manufacturing sites	10/02/2015	30/03/2015	Annex II	
IAIN/0073/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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	20/01/2015	30/03/2015	SmPC, Labelling and PL	
IAIN/0070	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	24/10/2014	n/a		
PSUV/0069	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0067	Change in the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of	24/07/2014	n/a		Change in the manufacturing process of the active substance

	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				
IB/0068/G	This was an application for a group of variations. 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	26/06/2014	n/a		
II/0065	Change in the manufacturing process of the finished product. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	25/04/2014	n/a		
PSUV/0062	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0058/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of SmPC to reflect efficacy and safety data obtained from clinical studies C10-003, C10-004 and long-term data obtained from studies C08-002A/B and	20/02/2014	21/03/2014	SmPC and PL	This submission provides data from two prospective studies (C10-003 and C10-004). The study C10-003 was an open-label, non-randomised, single-arm, multi-centre clinical trial of eculizumab in paediatric patients (one month up to 18 years) with aHUS. A total of 22 paediatric patients were treated with eculizumab in this study. The study C10-004

	C08-003A/B. The section 4 of the Package Leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				was an open-label, non-randomised, single-arm, multi-centre clinical trial of eculizumab in patients with aHUS that were at least 18 years of age or older. A total of 44 patients signed informed consent and 41 patients were treated in this study. In addition, long-term data from Studies C08-002A/B and C08-003A/B supporting the sustainability of response and the long-term clinical benefit of eculizumab therapy have been submitted. The SmPC has been updated to reflect these new safety and efficacy data. The section 4 of the Package Leaflet was updated accordingly.
II/0061	Submission of the results of a post-marketing multi-centre trial (M07-003) conducted to measure human anti-human antibodies to eculizumab in patients with paroxysmal nocturnal hemoglobinuria (MEA 021.3). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/02/2014	n/a		M07-003 was a non-therapeutic clinical study in paroxysmal nocturnal haemoglobinuria (PNH) patients who had previously participated in the E05-001 protocol (a phase III, long-term safety and efficacy study of Soliris in which all patients enrolled in the eculizumab trials in PNH were enrolled). 75 out of 187 patients from E05-001 were enrolled in M07-003 study and 74 were eligible for the study and had samples tested for the presence of HAHA using a validated HAHA assay. Results showed that none of the 74 patients tested positive for immune response to eculizumab following treatment for at least 6 years. The safety profile was in line with information already reflected in SmPC.
IB/0064	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	27/01/2014	n/a		

II/0060/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.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	23/01/2014	n/a		
II/0059/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	23/01/2014	n/a		
PSUV/0057	Periodic Safety Update	24/10/2013	18/12/2013	SmPC, Annex II and PL	Update of section 4.8 of the SmPC to add the adverse reaction Aspergillus infections. The Package leaflet is updated accordingly. Please refer to: Soliris-H-C-791-PSUV-0057 EPAR - Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IB/0056	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	06/12/2013	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/09/2013	18/12/2013	PL	
II/0054/G	This was an application for a group of variations. Addition of a manufacturing site for the finished product, addition of a site where batch control/testing takes place, change in supplier of packaging components. 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, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	25/07/2013	n/a		
II/0053	To introduce changes in test procedures for the active substance and drug product. B.I.b.2.d - Change in test procedure for AS or	25/07/2013	n/a		

	starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS				
II/0052/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.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.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	27/06/2013	18/12/2013	Annex II	
II/0050	Extension of indication of Soliris in the Paroxysmal Nocturnal Hemoglobinuria (PNH) in children. Consequently, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Soliris to include dose recommendations and additional information available in paediatric patients with PNH as requested by CHMP further to the assessment of ME2 14.2. The Package leaflet has been updated accordingly.	21/03/2013	29/04/2013	SmPC, Annex II and PL	Please refer to Scientific Discussion H-791-VAR-en.

	In addition, the MAH took the opportunity to introduce some editorial changes and to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 8.3. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0051	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	09/04/2013	n/a		
II/0045/G	This was an application for a group of variations. Changes in test methods for the active substance Change to the quality control arrangements for the active substance B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS 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	15/11/2012	n/a		

	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				
II/0047	Addition of a manufacturer for a starting material used in the manufacturing process of the active substance. B.I.a.1.d - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New manufacturer of material for which an assessment is required of viral safety and/or TSE risk	20/09/2012	n/a		
IB/0044	B.II.b.2.z - Change to batch release arrangements and quality control testing of the FP - Other variation	30/08/2012	n/a		
IA/0049	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	15/08/2012	n/a		
IA/0048/G	This was an application for a group of variations. 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 B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	01/08/2012	n/a		

IB/0043	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	25/07/2012	n/a		
IA/0042	A.7 - Administrative change - Deletion of manufacturing sites	09/07/2012	n/a		
R/0035	Renewal of the marketing authorisation.	15/03/2012	18/06/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Soliris continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. The renewal requires amendments to the terms of the Community Marketing Authorisation. The following annexes have been amended: I, II, IIIA, IIIB and annex 127a.
A20/0036	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).	16/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/791/A-20/0036

II/0038/G	This was an application for a group of variations. Addition of a manufacturing site for the finished product. Change to batch release arrangements and quality control testing of the finished product. Change in immediate packaging of the finished product. 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, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical method B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products	16/02/2012	13/04/2012	Annex II and PL	
IB/0040	B.II.f.1.d - Stability of FP - Change in storage	21/03/2012	04/10/2012	SmPC and PL	

	conditions of the finished product or the diluted/reconstituted product				
IA/0041	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	16/03/2012	n/a		
IA/0039	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	20/02/2012	n/a		
IB/0037	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	06/01/2012	n/a		
IB/0033	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	15/12/2011	n/a		
IB/0032	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	30/11/2011	n/a		
IB/0031	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	30/11/2011	n/a		

IAIN/0034/G	This was an application for a group of variations. C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities 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 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.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	28/11/2011	n/a		
II/0027	Extension of indication of Soliris in the treatment of atypical haemolytic uremic syndrome (aHUS). Consequently sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Summary of Product Characteristics (SmPC) have been updated. In addition additional vaccination and antibiotic prophylaxis recommendation are reflected in sections 4.4 and 6.6 of the SmPC. The PL has been updated accordingly. Furthermore the MAH took the opportunity to update the product information with the latest version of the QRD template.	22/09/2011	24/11/2011	SmPC, Annex II and PL	Please refer to Scientific Discussion: Soliris-H-791-II-27-AR

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0030/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 - Tightening of in-process limits B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	16/11/2011	n/a		
II/0028	Change in the manufacturing process and change of specifications for raw materials. B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	22/09/2011	22/09/2011		
IB/0026	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	30/03/2011	n/a		
II/0025	This type II variation concerns an update of section 4.4 of the SmPC to include information regarding the risk of meningococcal infections as requested by the	17/02/2011	24/03/2011	SmPC, Annex II and PL	Cumulatively 12 cases of meningococcal infections have been received in the Alexion Pharmacovigilance post-marketing safety database. The respective statement in

	CHMP following the assessment of PSUR 5 and revision of section 4.8 to include post-marketing experience. In addition, the PL has been revised to align the safety information with the SmPC. Furthermore, the PL is brought in line with the latest version of the QRD template (version 7.3.1), the version number of the DDPS was deleted and the version number of the RMP was updated in Annex II, and the list of the local representatives in the PL is amended. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				section 4.4 of the SmPC has therefore been updated. In addition, following a review of the post-marketing safety database, an update of the ADRs listed in section 4.8 was considered necessary. Finally, the PL has been updated to align the safety information with the SmPC.
II/0024	Changes to the manufacture and control of the active substance 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 medicinal product and is not related to a protocol	18/11/2010	25/11/2010		
IB/0023	B.II.b.z - Change in manufacture of the Finished Product - Other variation	23/09/2010	n/a		
IA/0022	A.7 - Administrative change - Deletion of manufacturing sites	24/06/2010	n/a	Annex II	
II/0019	New facility for the testing of the drug susbtance B.I.a.1.e - Change in the manufacturer of AS or of a	20/05/2010	27/05/2010		

	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				
IB/0021	Change to the control of the drug susbtance 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	17/05/2010	n/a		
II/0018	Changes to the manufacturing process of the active substance 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 medicinal product and is not related to a protocol	22/04/2010	27/04/2010		
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/2010	n/a	PL	
II/0013	Additional site for the manufacture of the drug substance with consequential site-specific adaptations to the drug substance manufacturing process Change(s) to the manufacturing process for the active substance	19/11/2009	21/12/2009	Annex II	

II/0016	Changes to eculizumab reference standard Change(s) to the test method(s) and/or specifications for the active substance	24/09/2009	05/10/2009		
II/0012	Changes to in-process controls for the active substance manufacturing process. Changes to the specifications of the active substance and finished product. Change(s) to the test method(s) and/or specifications for the active substance	23/07/2009	29/07/2009		
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/06/2009	n/a	PL	
II/0004	Update of DDPS (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	19/03/2009	28/05/2009	Annex II	This type II variation concerned an update of the Detailed Description of the Pharmacovigilance System (DPPS). Consequently, Annex II has been updated to include the new version number of the agreed DDPS (version 4.0). In addition, standard text has been added to Annex II to reflect the latest version of the Risk Management Plan (RMP) agreed with CHMP.
II/0003	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/03/2009	28/05/2009	SmPC, Annex II, Labelling and PL	This type II variation concerns an update of section 4.8 of the SPC, as requested by CHMP following the assessment of the 2nd PSUR, with the addition of the ADR 'meningococcal infection'. Further, the MAH has included a table in section 4.8 with all adverse drug reactions observed in clinical trials instead of the current table which includes adverse drug events. The Package Leaflet has been updated accordingly.

					The MAH has also made minor editorial changes to the annexes to put them in line with the latest QRD template and updated the list of local representatives in the Package Leaflet. In addition, the MAH took the opportunity to make minor changes to the wording of the 'conditions or restrictions with regard to the safe and effective use of the medicinal product' in annex II for increased clarity, as agreed with CHMP following the assessment of FUM 022. As a consequence, Annex IV has been updated accordingly.
IB/0014	IB_38_c_Change in test procedure of finished product - other changes	28/05/2009	n/a		
IA/0011	IA_01_Change in the name and/or address of the marketing authorisation holder	27/04/2009	n/a	SmPC, Labelling and PL	
II/0007	Change of method used for release and stability testing of the active substance and finished product. Change(s) to the test method(s) and/or specifications for the active substance	19/03/2009	03/04/2009		
II/0005	Additional manufacturing site for the drug product. Change(s) to the manufacturing process for the finished product	19/02/2009	03/03/2009		
IB/0009	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	04/02/2009	n/a	SmPC	
IA/0008	IA_09_Deletion of manufacturing site	09/01/2009	n/a		

II/0002	Change(s) to the test method(s) and/or specifications for the active substance	26/06/2008	08/07/2008		
II/0001	Change(s) to the manufacturing process for the active substance	13/12/2007	13/12/2007		