Ultomiris

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/0045	Update of sections 4.8 and 5.1 of the SmPC in order to update the summary of safety profile and information in adult patients with Generalised Myasthenia Gravis based on final results from study ALXN1210-MG-306; this is a Phase 3, randomized, double-blind, parallel-group, placebo-controlled,	26/09/2024		SmPC	Section 4.8: The frequency of the ADR is updated based on pooled safety data. In Section 5.1 Generalised Myasthenia Gravis (gMG) under Study in adult patients with gMG and for study ALXN1210-MG-306 it is confirmed that: "in the Open Label extension study the treatment effect is sustained for 164 weeks".

[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).

	multi-center study with an ongoing Open-Label Extension Period of up to 2 years in adult patients with gMG who were naïve to complement inhibitor treatment. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI is recommended for approval. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Furthermore, it is added that: "In patients who initially received placebo during the 26-week Randomised-Controlled Period and initiated treatment with ULTOMIRIS during the Open-Label Extension Period, a rapid and sustained treatment response on all endpoints including MG-ADL and QMG was observed over a median treatment duration of approximately 2 years". Also it is inserted that: "At the end of the Open-Label Extension Period (median duration of ULTOMIRIS treatment both during Randomised-Control Period and Open-Label Extension was 759 days), 30.1% of patients decreased their daily dose of corticosteroid therapy and 12.4% of patients stopped corticosteroid therapy". For more information, please refer to the Summary of Product Characteristics.
II/0043/G	This was an application for a group of variations. A grouped application comprised of a Type II Variation and a Type IA Variation, as follows: Type II (C.I.4): Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update clinical information regarding the atypical haemolytic uremic syndrome (aHUS) indication, based on final results from studies ALXN1210-aHUS-311 and ALXN1210-aHUS-312. ALXN1210-aHUS-311 is a phase 3, open-label, uncontrolled, multicenter, single treatment arm study in adolescent and adult patients with evidence of TMA who are naïve to complement inhibitor treatment, while ALXN1210- aHUS-312 is a phase 3,	26/09/2024		SmPC and PL	SmPC new text: Section 4.4 for Paediatric Population with Atypical haemolytic uremic syndrome (aHUS) it is added that: "The most common adverse reactions (> 20%) reported in paediatric patients were pyrexia, vomiting, diarrhoea, headache, nasopharyngitis, upper respiratory tract infection and abdominal pain." Section 5.1 update of the ATC code to L04J02 An extensive update of study results for Atypical haemolytic uremic syndrome (aHUS) in adults (ALXN1210-aHUS-311) and paediatric patients (ALXN1210 aHUS 312) The final efficacy analysis for the studies on all adult and

	open-label, uncontrolled, multicenter, single treatment arm study in pediatric patients with evidence of TMA who are naïve to complement inhibitor treatment (Cohort 1) or are clinically stable after having been treated with eculizumab (Cohort 2). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. Type IA (A.6): To change the ATC Code for ravulizumab from L04AA43 to L04AJ02. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data A.6 - Administrative change - Change in ATC Code/ATC Vet Code				paediatric patients treated with ravulizumab over a median treatment duration of 130.36 weeks confirmed that ravulizumab treatment responses observed during the Primary Evaluation Period were maintained throughout the duration of the study. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10787 /202312	Periodic Safety Update EU Single assessment - ravulizumab	11/07/2024	n/a		PRAC Recommendation - maintenance
IB/0046/G	This was an application for a group of variations. C.I.7.a - Deletion of - a pharmaceutical form C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/07/2024		SmPC, Annex II, Labelling and PL	
II/0041	Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update the frequency of adverse reactions and to update pharmacokinetic, efficacy and safety information on PNH based on final results from	30/05/2024		SmPC and PL	SmPC new text: Black triangle is removed. Section 4.4 (IV formulation): New text is added in line with the SC formulation

	studies ALXN1210-PNH-304, ALXN1210-PNH-301 (listed as a category 3 study in the RMP), ALXN1210-PNH-201 and ALXN1210-PNH-103. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring section 4.5 of the IV formulation with that of the SC formulation and remove the black triangle in line with the outcome of the recent renewal procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				"Chronic intravenous human immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as ravulizumab and thereby decrease serum ravulizumab concentrations." Section 4.8 AE summary listing and frequencies are being updated Section 5.1 Results of the long-term extension period for PNH studies were added confirming that responses are maintained throughout the duration of studies. Section 5.2 (SC formulation) Estimated central volume is added in table 11. For more information, please refer to the Summary of Product Characteristics.
R/0040	Renewal of the marketing authorisation.	22/02/2024	19/04/2024		Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Ultomiris in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0042/G	This was an application for a group of variations. B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.II.g.3 - Deletion of an approved change management protocol related to the finished product	24/01/2024	n/a		
II/0039	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	31/08/2023	n/a		

PSUSA/10787 /202212	Periodic Safety Update EU Single assessment - ravulizumab	31/08/2023	n/a		PRAC Recommendation - maintenance
II/0034	Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study ALXN1210-PNH-302, a Phase III, randomised, open-label, active controlled study of ALXN1210 versus eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) currently treated with eculizumab, listed as a category 3 study in the RMP. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/07/2023	19/04/2024	SmPC and PL	SmPC new text Section 4.8 The frequency of the most common AE has been updated and the following AE are also switched from common to very common: pyrexia, nausea, arthralgia, fatigue, back pain, and abdominal pain. Section 5.1 It was added that "The final efficacy analysis for the study included all patients ever treated with ravulizumab (n=192) and had a median treatment duration of 968 days".
IB/0038/G	This was an application for a group of variations. B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.II.g.3 - Deletion of an approved change management protocol related to the finished product	23/06/2023	n/a		
X/0027/G	This was an application for a group of variations. Extension application to introduce a new pharmaceutical form (solution for injection) associated with new strength (245 mg) and route of administration (subcutaneous use), grouped with a type II variation (C.I.4) to align the Summary of	30/03/2023	31/05/2023	SmPC, Labelling and PL	Not applicable

	product characteristics and Labelling of Ultomiris intravenous formulation (IV) with the proposed Ultomiris subcutaneous formulation (SC). The RMP (version 7.0) is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.3. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(e) Change or addition of a new route of administration C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0037/G	This was an application for a group of variations. B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.II.g.3 - Deletion of an approved change management protocol related to the finished product	25/05/2023	n/a		
II/0032	Extension of indication to include the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody-positive, based on interim results from study ALXN1210-NMO-307; this is a phase 3, external placebo-controlled, open-label, multicenter study to evaluate the efficacy and safety of	30/03/2023	05/05/2023	SmPC and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0032

	ravulizumab in adult patients with NMOSD. 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 6.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0035/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible 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.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)	17/03/2023	05/05/2023	Annex II and PL	
II/0033/G	This was an application for a group of variations. 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	24/11/2022	n/a		

	control/testing takes place 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				
II/0030	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	06/10/2022	05/05/2023	Annex II	
II/0026	Extension of indication to include treatment of adult patients with generalized myasthenia gravis (gMG). As a consequence, Sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 and 6.6 of the SmPC and corresponding sections in the Package Leaflet are updated accordingly. The RMP has been updated to version 4.0 to align with the indication extension. Lastly, the minor editorial corrections are made throughout the SmPC and package leaflet. The Applicant also requested 1 year of market protection for a new indication (Article 14(11) of Regulation (EC) 726/2004). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/07/2022	21/09/2022	SmPC and PL	Please refer to Scientific Discussion: EMEA/H/C/004954/II/0026

II/0029	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	01/09/2022	n/a		
PSUSA/10787 /202112	Periodic Safety Update EU Single assessment - ravulizumab	01/09/2022	n/a		PRAC Recommendation - maintenance
IB/0031	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	17/08/2022	n/a		
PSUSA/10787 /202106	Periodic Safety Update EU Single assessment - ravulizumab	27/01/2022	01/04/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10787/202106.
IB/0025/G	This was an application for a group of variations. B.II.g.3 - Deletion of an approved change management protocol related to the finished product B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	16/11/2021	n/a		
II/0016	Update of section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects of the SmPC, with consequential updates to Section 2 and 4 of the Patient Information Leaflet regarding anaphylactic reaction, hypersensitivity, and infusion-related reactions.	30/09/2021	01/04/2022	SmPC and PL	SmPC new text: Administration of ravulizumab may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). 'Anaphylactic reaction and hypersensitivity' have been added to the Table of Adverse reactions as uncommon

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				adverse reactions. 'Infusion related reaction' has been added to the Table of Adverse reactions as common adverse reaction.
II/0010	Extension of indication for Ultomiris to include treatment of paroxysmal nocturnal haemoglobinuria (PNH) in paediatric patients with a body weight of 10 kg or above; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, Annex II is updated to reflect the agreed educational material (addition of a "Parent guide"). Version 2.1 of the RMP has also been submitted, in order to include the new indication. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/07/2021	01/09/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Ultomiris-H-C-004954-II-0010'
IB/0023/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	18/08/2021	n/a		
IAIN/0022/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release	13/07/2021	01/09/2021	SmPC, Annex II and PL	

	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.f.1.a.3 - Stability of FP - Reduction of the shelf life of the finished product - After dilution or reconstitution				
PSUSA/10787 /202012	Periodic Safety Update EU Single assessment - ravulizumab	08/07/2021	n/a		PRAC Recommendation - maintenance
IB/0021/G	This was an application for a group of variations. B.I.e.3 - Deletion of an approved change 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	28/06/2021	n/a		
II/0015/G	This was an application for a group of variations. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	24/06/2021	n/a		
IB/0020	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/06/2021	n/a		
IB/0019	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	21/05/2021	n/a		

	re-test period/storage period supported by real time data				
IAIN/0017/G	This was an application for a group of variations. B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data B.II.g.3 - Deletion of an approved change management protocol related to the finished product	29/04/2021	n/a		
IB/0014/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	22/04/2021	n/a		

IB/0011/G	This was an application for a group of variations. B.II.g.3 - Deletion of an approved change management protocol related to the finished product B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product 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	27/01/2021	n/a		
IB/0012	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	18/01/2021	n/a		
PSUSA/10787 /202006	Periodic Safety Update EU Single assessment - ravulizumab	14/01/2021	n/a		PRAC Recommendation - maintenance
X/0004/G	This was an application for a group of variations. Extension application to add a new strength (1100 mg in 11 ml vial, concentration 100 mg/ml) for Ultomiris concentrate for solution for infusion, grouped with a Type II application (B.II.z) for a new presentation (300 mg in 3 ml vial, concentration 100 mg/ml) including changes in the active substance concentration, excipients composition and concentrations, and minor differences in the last two steps of the manufacturing process.	17/09/2020	18/11/2020	SmPC, Annex II, Labelling and PL	

	Annex I_2.(c) Change or addition of a new strength/potency B.II.z - Quality change - Finished product - Other variation				
IB/0009/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.g.3 - Deletion of an approved change management protocol related to the finished product	23/09/2020	01/09/2021	SmPC	
PSUSA/10787 /201912	Periodic Safety Update EU Single assessment - ravulizumab	09/07/2020	n/a		PRAC Recommendation - maintenance
II/0002	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/04/2020	25/06/2020	SmPC, Annex II and PL	
IB/0007	B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	22/06/2020	n/a		
II/0005	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	28/05/2020	n/a		
II/0003/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	16/01/2020	25/06/2020	SmPC	

	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				
IAIN/0001	A.1 - Administrative change - Change in the name and/or address of the MAH	26/07/2019	25/06/2020	SmPC, Labelling and PL	