Praluent

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/0088/G	This was an application for a group of variations. 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)	30/01/2024		Annex II	

[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).

	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				
IB/0086	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	04/12/2023	n/a		
IAIN/0087	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	29/11/2023		SmPC	
IB/0085	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	22/11/2023	n/a		
II/0081	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	16/11/2023	n/a		
II/0078	Extension of indication to include treatment of paediatric patients 8 years of age and older with heterozygous familial hypercholesterolemia (HeFH) as an adjunct to diet, alone or in combination with other LDL-C lowering therapies, based on final results from study EFC14643 listed as a category 3 study in the RMP; this is a randomized, double-blind, placebo-controlled study followed by an open-label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia. As a	12/10/2023	15/11/2023	SmPC and PL	Please refer to Scientific Discussion ‘EMEA/H/C/003882/II/0078

	consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP was agreed during the procedure. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0084/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.e - Stability of FP - Change to an approved stability protocol B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) A.7 - Administrative change - Deletion of manufacturing sites	11/10/2023	n/a		
IB/0082	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	31/07/2023	n/a		

N/0083	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2023	15/11/2023	PL	
IB/0080/G	This was an application for a group of variations. 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.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability 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 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	31/05/2023	n/a		
IB/0079	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	16/05/2023	n/a		
II/0077	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	09/02/2023	n/a		

	of studies to the competent authority				
T/0076	Transfer of Marketing Authorisation	18/11/2022	16/12/2022	SmPC, Labelling and PL	
IB/0075/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	15/12/2022	n/a		
IA/0074	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	10/10/2022	n/a		
II/0072	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/09/2022	n/a		
IB/0073	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	16/08/2022	n/a		

IB/0071	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/07/2022	n/a		
II/0068	Update of section 4.8 of the SmPC, based on the final results from category 3 study OBS14697; a non-interventional, retrospective drug utilisation study that was designed to assess in Europe the effectiveness of the dosing recommendation and to describe patterns of alirocumab utilization in real world clinical practice. In addition, the MAH took the opportunity to implement editorial changes in SmPC and package leaflet. The submission of the study report addresses the Post-Authorisation Measure MEA/FSR 019.8. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/06/2022	28/11/2022	SmPC and PL	Study OBS14697 is a non-interventional drug utilisation study to assess in Europe the effectiveness of the dosing recommendation included in the SmPC to avoid very low LDL-C levels. In the drug utilisation study, it has been shown that the EU SmPC was well understood and followed by the physicians prescribing alirocumab, and that compliance to the EU SmPC allowed to prevent the occurrence of very low LDL-C levels in most of the patients, while a substantial number of the patients met the therapeutic goal of LDL-C reduction. However, although adverse consequences of very low LDL-C data were not identified in in alirocumab studies, data on the long-term effects of very low levels of LDL-C are overall limited and the MAH was asked to retain the sentence reflecting that the long-term effects of sustained very low levels of LDL-C are unknown in the SmPC. Section 4.8. of the SmPC was updated to remove the increased risk of new onset of diabetes associated with lower levels of LDL-C.
IB/0070	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	25/05/2022	n/a		
PSUSA/10423 /202107	Periodic Safety Update EU Single assessment - alirocumab	10/02/2022	n/a		PRAC Recommendation - maintenance
IA/0069	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	11/01/2022	n/a		

IB/0067/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.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	06/01/2022	n/a		
II/0065	Update of section 5.1 of the SmPC in order to include information on the effect of alirocumab on the neurocognitive function based on final results from the study R727-CL-1532 listed as a category 3 study in the RMP; this is an interventional study to evaluate the neurocognitive function during the treatment, as well as the effect of the medicinal product in comparison with placebo on lipoproteins and to assess the safety and tolerability. The RMP version 6.0 has also been submitted. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.2 and to update the list of local representatives. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/12/2021	28/11/2022	SmPC	The SmPC section 5.1 was updated with results from a 96 week, randomized, double-blinded, placebo-controlled trial evaluated the effect of alirocumab on neurocognitive function after 96 weeks of treatment (~2 years) in patients with heterozygous familial hypercholesterolemia (HeFH) or non-familial hypercholesterolemia at high or very high cardiovascular risk. For more information, please refer to the Summary of Product Characteristics.
IB/0064/G	This was an application for a group of variations.	17/06/2021	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - 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) B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IB/0063/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/03/2021	n/a		
PSUSA/10423 /202007	Periodic Safety Update EU Single assessment - alirocumab	11/02/2021	n/a		PRAC Recommendation - maintenance
II/0058/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.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits	14/01/2021	n/a		

	applied during the manufacture of the AS - Other variation B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0062/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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	06/01/2021	n/a		
IB/0060	B.II.f.1.b.5 - Stability of FP - Extension of the shelf	14/12/2020	15/11/2021	SmPC and PL	

	life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol				
II/0059	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology recommendations, the undesirable effects section and pharmacokinetic and pharmacodynamic sections with information on paediatric population, based on final results from study EFC14660, a category 3 open-label study in the RMP, to evaluate the efficacy and safety of alirocumab in children and adolescents with homozygous familial hypercholesterolemia; 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	12/11/2020	15/11/2021	SmPC and PL	Study EFC14660 had an exploratory nature, as per the Paediatric Investigation Plan (PIP) and was designed and conducted to evaluate the efficacy and safety of alirocumab in a paediatric population (8 to 17 years of age) with hoFH. The results thereof imposed updates on relevant sections of the SmPC in order update data on children and adolescents with homozygous familial hypercholesterolemia. For more information, please refer to the Summary of Product Characteristics.
X/0054/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within	25/06/2020	19/08/2020	SmPC, Annex II, Labelling and PL	

	the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging				
II/0056/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	05/06/2020	n/a		

	manufacturer of a novel excipient B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				

R/0055	Renewal of the marketing authorisation.	26/03/2020	02/06/2020	SmPC, Annex II, Labelling and PL	
IB/0057	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	23/04/2020	n/a		
II/0053	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/03/2020	n/a		
PSUSA/10423 /201907	Periodic Safety Update EU Single assessment - alirocumab	13/02/2020	n/a		PRAC Recommendation - maintenance
II/0050/G	This was an application for a group of variations. 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 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 C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	16/01/2020	n/a		

	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				
II/0051	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/12/2019	02/06/2020	SmPC and PL	
IB/0048/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 B.I.a.z - Change in manufacture of the AS - Other variation 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.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	28/11/2019	n/a		

	material/intermediate/reagent - Other variation				
II/0049/G	This was an application for a group of variations. 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.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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/11/2019	n/a		
IB/0047/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other	31/10/2019	02/06/2020	SmPC	

	variation				
IB/0045/G	This was an application for a group of variations. 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.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.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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	07/06/2019	n/a		
IB/0046/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/05/2019	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0042	Extension of Indication to include treatment of adults with established atherosclerotic cardiovascular disease to reduce the risk of major adverse cardiovascular events by lowering LDL-C levels, as an adjunct to correction of other risk factors, in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. The final study report of Study EFC11570 was provided in support of the application; a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of alirocumab on the occurrence of cardiovascular events in patients who have recently experienced an acute coronary syndrome. As a consequence, sections, 4.1, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, an updated RMP version 4.2 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	31/01/2019	11/03/2019	SmPC and PL	Please refer to Scientific Discussion 'Praluent-H-C-3882-II-42'.
PSUSA/10423 /201807	Periodic Safety Update EU Single assessment - alirocumab	14/02/2019	n/a		PRAC Recommendation - maintenance

II/0041	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/11/2018	n/a		
IAIN/0043	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	18/09/2018	12/12/2018	Annex II and PL	
II/0040	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/09/2018	n/a		
IB/0039	C.I.3.z - 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 - Other variation	25/06/2018	12/12/2018	SmPC and PL	
IB/0038/G	This was an application for a group of variations. 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 B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	05/06/2018	n/a		
II/0037	C.I.13 - Other variations not specifically covered	26/04/2018	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0036	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	19/04/2018	n/a		
PSUSA/10423 /201709	Periodic Safety Update EU Single assessment - alirocumab	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0035	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	28/02/2018	n/a		
II/0032/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 control/testing takes place 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.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.b - Change to importer, batch release arrangements and quality control testing of the FP -	18/01/2018	n/a		

	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				
IB/0034	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	05/01/2018	n/a		
II/0030	B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	23/11/2017	n/a		
II/0028/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.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	16/11/2017	12/12/2018	Annex II, Labelling and PL	

	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB				
II/0029	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/11/2017	n/a		
IB/0031/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.1.z - Change in the specification parameters	06/11/2017	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
PSUSA/10423 /201703	Periodic Safety Update EU Single assessment - alirocumab	26/10/2017	n/a		PRAC Recommendation - maintenance
II/0021/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection 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.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. duplication of line) B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/09/2017	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0025	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	10/08/2017	n/a		
IB/0027/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	19/07/2017	n/a		
II/0024/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.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	13/07/2017	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0022/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation 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.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	01/06/2017	n/a		
IB/0023	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	10/05/2017	n/a		
PSUSA/10423 /201609	Periodic Safety Update EU Single assessment - alirocumab	06/04/2017	n/a		PRAC Recommendation - maintenance
IB/0020	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/03/2017	n/a		

II/0018	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/02/2017	n/a		The applicant has performed a phase I single blind (patient blinded) study to further investigate the lipid turnover in patients with mild elevated hypercholesterolemia. Overall, the results support the general mechanism of action and the expected effect of alirocumab. The limited safety data from the study are in line with the known safety profile of alirocumab. No changes to the mechanism of action are proposed as this is sufficiently described already in section 5.1 of the SmPC.
IB/0019	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/02/2017	n/a		
IB/0017	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	05/01/2017	n/a		
II/0014/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	08/12/2016	n/a		
IA/0015/G	This was an application for a group of variations.	01/12/2016	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0009/G	This was an application for a group of variations. Update of section 4.2 of the SmPC to include a 300 mg every 4 weeks dosing regimen, based on the results of study CHOICE I (MEA 005). Section 4.8, 5.1 and 5.2 of the SmPC and the PL have also been updated to reflect the study results. In addition, the MAH submitted the final study report of study CHOICE II (MEA 009) and additional analysis of the two studies. The MAH is also taking the opportunity the update the local representatives section of the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/10/2016	14/11/2016	SmPC and PL	The MAH proposed with this variation a new dose and dosing regimen of 300 mg every 4 weeks as an alternative for the 75 mg or 150 mg dose every 2 weeks. To support this submission the applicant has evaluated the pharmacokinetics (PK) of this dosing regimen in two exploratory phase 2 studies. The CHMP concluded that the 300 mg dose every 4 weeks was demonstrated to be generally safe and effective. The usual starting dose for Praluent remains 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg once every 2 weeks, or 300 mg once every 4 weeks (monthly), administered subcutaneously. The dose of Praluent can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 to 8 weeks after treatment initiation or titration, and dose adjusted accordingly (up-titration or down-titration). If additional LDL-C reduction is needed in patients treated with 75 mg once every 2 weeks or 300 mg once every 4 weeks (monthly), the dosage may be adjusted to the maximum dosage of 150 mg once every 2 weeks.
PSUSA/10423 /201603	Periodic Safety Update EU Single assessment - alirocumab	29/09/2016	n/a		PRAC Recommendation - maintenance

II/0012/G	This was an application for a group of variations. • II B.I.a.1. e: - To add Sanofi Chimie (9 Quai Jules Guesde 94403 Vitry-sur-Seine France) as an alternative manufacturing site for the manufacture of the formulated active substance alirocumab. • II B.I.a.1. j : - To add Sanofi Chimie (9 Quai Jules Guesde 94403 Vitry-sur-Seine France) as an alternative quality control testing site of the formulated active substance alirocumab. • IB B.I.b.2.e: - To change the analytical method used for quantification of DMSO impurity from HPLC to GC during the process performance qualification campaign. • IA B.1.b.2.a: - To use the kinetic chromogenic method as an alternative to the kinetic turbidimetric method for the Ph. Eur test procedure for bacterial endotoxin testing. • IA B.1.b.2.a: - To use the membrane filtration method as an alternative to pour plate method for bioburden testing on bioreactor cell culture pre-transfer samples. • IA B.I.c.3.b: - To replace the method for identification of polycarbonate bottles from NIR (donor site) to FTIR (receiving testing site). B.I.a.1.e - Change in the manufacturer of AS or of a	15/09/2016	14/11/2016	Annex II	

	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.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.c.3.b - Change in test procedure for the immediate packaging of the AS - Other changes to a test procedure (including replacement or addition)				
II/0006/G	This was an application for a group of variations. Submission of the clinical study report of EFC13672 (Efficacy and safety study of alirocumab versus placebo in Japanese patients with heFH or high CV risk patients with hypercholesterolemia not adequately controlled with LMT). This submission	15/09/2016	n/a		

	fulfils MEA007. Sanofi is also submitting 2 population PK study reports (POH0443 and POH0444) on pooled data from selected phase 1, phase 2 and phase 3 studies, which are provided for further estimation of PK parameters and to analyse the relationship between alirocumab concentrations and LDL-C concentrations in Japanese patients. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0013	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/08/2016	n/a		
II/0010/G	This was an application for a group of variations. Update of section 5.1 of the SmPC to reflect the availability of long term efficacy data, based on study EFC11569. In addition, second-step analysis study reports have been submitted for studies LTS11717, EFC12492, R727-CL-1112 and EFC12732 (as per MEAs 001, 002, 003, 004 and 006).	21/07/2016	14/11/2016	SmPC	The MAH submitted additional follow-up information related to the 5 phase 3 extension studies that have been completed since the initial marketing authorization application with 75 mg and 150 mg every 2 weeks as a dosing regimen. The studies, conducted in patients with heterozygous familial hypercholesterolaemia (heFH) (FH I, FH II, HIGH FH), in patients at high risk of atherosclerotic

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				cardiovascular disease (CVD) (COMBO II), and in both heFH patients and patients at high risk of atherosclerotic CVD (LONG TERM), are now completed and results of the second step analysis were presented. These results consist of the analysis of the efficacy endpoints beyond Week 52, ie, up to Week 78 (FH I, FH II, HIGH FH, and LONG TERM), and up to Week 104 (COMBO II). The data presented on the 5 finalised studies shows a substantial increase in patients exposed to alirocumab, increasing the cumulative exposure to alirocumab to 4029 patient-years (as compared with 3451 patient-years in the initial MAA). The additional safety data with longer exposure are consistent with those reported in the initial MAA and support the benefit risk profile identified at that time.
II/0007	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	14/07/2016	n/a		
II/0005	To change the storage conditions for the 75mg/ml and 150 mg/ml solution for injection in pre-filled pen and in pre-filled syringe (EU/1/15/1031/001-012). B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	16/06/2016	14/11/2016	SmPC, Labelling and PL	

IB/0008/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits	15/06/2016	n/a		

	applied during the manufacture of the AS - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.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				
IB/0004/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	08/04/2016	n/a		

	authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
N/0003	Update of the package leaflet with revised contact details of the local representatives for Italy, Lithuania, and Hungaria. In addition the MAH took the opportunity to make linguistic amendments to annex IIIA and IIIB of the Romanian, Greek, Hungarian, Italian, Danish, Spanish and French annexes. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/03/2016	14/11/2016	PL	
IA/0002/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.4.a - Change to in-process tests or limits	10/03/2016	n/a		

	applied during the manufacture of the AS - Tightening of in-process limits 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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits				
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/11/2015	14/11/2016	Labelling and PL	