Repatha

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IG/1743	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	28/06/2024		Annex II	
PSUSA/10405	Periodic Safety Update EU Single assessment -	07/03/2024	n/a		PRAC Recommendation - maintenance

[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).

/202307	evolocumab				
IB/0071	B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue	26/02/2024	n/a		
IB/0070/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.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	26/02/2024	n/a		
IB/0068	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	07/12/2023	n/a		
IB/0066	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	23/05/2023	n/a		
II/0061	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/03/2023	27/03/2024	SmPC	

IA/0065/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	09/11/2022	n/a		
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2022	30/01/2023	Labelling	
IB/0063/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/10/2022	n/a		
IB/0062	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	10/10/2022	n/a		
IB/0059	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/09/2022	n/a		
IB/0060/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.a - Change in the manufacturing process of	07/09/2022	n/a		

	the finished or intermediate product - Minor change in the manufacturing process				
II/0058	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/04/2022	30/01/2023	SmPC	
II/0057	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/02/2022	30/01/2023	SmPC	
II/0049/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/10/2021	26/11/2021	SmPC and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-49G'
IB/0056	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/09/2021	n/a		
IB/0053	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/07/2021	n/a		
WS/2026	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	08/07/2021	n/a		

	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				
IB/0054	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	30/06/2021	n/a		
IAIN/0055	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	18/06/2021	n/a		
II/0051	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	22/04/2021	n/a		
PSUSA/10405 /202007	Periodic Safety Update EU Single assessment - evolocumab	25/02/2021	21/04/2021	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10405/202007.
II/0048	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/03/2021	n/a		
IB/0050/G	This was an application for a group of variations.	09/03/2021	n/a		

	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.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 material/intermediate/reagent - Other variation				
II/0047	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	11/02/2021	21/04/2021	SmPC and PL	
II/0044	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	14/01/2021	21/04/2021	Annex II	
II/0043	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	29/10/2020	21/04/2021	SmPC	

IB/0045	B.IV.1.z - Change of a measuring or administration device - Other variation	21/07/2020	21/04/2021	PL	
IAIN/0042	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	11/05/2020	n/a		
R/0040	Renewal of the marketing authorisation.	30/01/2020	14/04/2020		Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Repatha in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10405 /201907	Periodic Safety Update EU Single assessment - evolocumab	13/02/2020	n/a		PRAC Recommendation - maintenance
II/0038	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/01/2020	14/04/2020	SmPC and PL	
IB/0041/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.II.z - Quality change - Finished product - Other variation	19/12/2019	n/a		
PSUSA/10405 /201901	Periodic Safety Update EU Single assessment - evolocumab	19/09/2019	19/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10405/201901.
II/0036	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	12/09/2019	n/a		
II/0033	Update of section 4.8 of the SmPC in order to update the safety information with regards to the adverse reaction "Influenza-like illness" with a frequency of Uncommon following the assessment of influenza-like illness with evolocumab in both the clinical database and postmarketing database. The Package Leaflet Section 4 was updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement changes to the package leaflet Section 2 subsequent to the revised Annex to the EC guideline on excipients in the labelling (EMA/CHMP/302620/2017) to update the wording for sodium. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/09/2019	19/11/2019	SmPC and PL	Signal evaluation of influenza-like illness using the MAH's clinical trial database was conducted. Furthermore, a search of the MAH's Global Safety Database was also performed to identify all cases with the preferred terms influenza and influenza-like illness. Influenza-like illness manifests as similar symptoms to influenza and may be due to a non-influenza virus (eg, rhinovirus, adenovirus) or could be associated with the use of medications. The MAH received 3122 post marketing events of influenza and influenza-like illness, of which 165 events were reported as serious. Of the 165 serious events, 24 cases reported a positive re-challenge that was suggestive of a possible causal drug-event association. Of the 24 cases, 19 reported influenza-like-illness and 5 reported influenza. All were classified as serious events. The 19 cases of influenza-like-illness show a probable association with the use of evolocumab due to e.g. re-challenge and plausible time to onset. Based on the 19 post marketing cases which reported influenza-like illness with a probable causality the proposal of the MAH to include influenza-like-illness as an adverse event with frequency 'uncommon' in section 4.8 was accepted.
II/0035/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	25/07/2019	19/11/2019	SmPC	

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0037	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	15/07/2019	n/a		
II/0031	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	19/11/2019	SmPC and Labelling	
PSUSA/10405 /201807	Periodic Safety Update EU Single assessment - evolocumab	28/02/2019	29/04/2019		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10405/201807.
II/0026/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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	11/04/2019	n/a		

IB/0032	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	04/01/2019	n/a		
II/0028	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	29/11/2018	n/a		
IAIN/0030	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	26/10/2018	n/a		
PSUSA/10405 /201801	Periodic Safety Update EU Single assessment - evolocumab	06/09/2018	n/a		PRAC Recommendation - maintenance
IG/0946	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	04/06/2018	29/04/2019	PL	
II/0017/G	This was an application for a group of variations. Extension of the indication to adult patients with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors based on the results of the FOURIER study. As a consequence sections 4.1, 4.2, 4.4 4.8, 5.1 and	22/03/2018	08/05/2018	SmPC and PL	Please refer to the Scientific Discussion Repatha (EMEA/H/C/3766/II/017/G).

	5.2 of the SmPC were updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 5.1 of the SmPC to include the effects of evolocumab on atherosclerotic disease burden as measured by intravascular ultrasound based on Study 20120153 (GLAGOV study). The RMP is updated to version 2.5 in order to add two category 3 studies (Study 20160250 and Study 20150338), as well as to update the milestones of five category 3 studies (20110110, 20110271, 20120138, 20130286, 20130295). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one 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.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 authorisation, including the RMP - Other variation				
IB/0022	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	25/04/2018	n/a		
IB/0023	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	16/04/2018	n/a		
IB/0021	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	02/03/2018	19/04/2018	SmPC	
PSUSA/10405 /201707	Periodic Safety Update EU Single assessment - evolocumab	08/02/2018	n/a		PRAC Recommendation - maintenance

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	05/01/2018	n/a		
IG/0853	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	10/11/2017	19/04/2018	Annex II and PL	
PSUSA/10405 /201701	Periodic Safety Update EU Single assessment - evolocumab	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0016	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	16/06/2017	n/a		
IAIN/0014/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.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	07/04/2017	19/04/2018	Annex II and PL	
X/0002	Annex I_2.(c) Change or addition of a new strength/potency	15/12/2016	17/02/2017	SmPC, Annex II, Labelling	

				and PL	
PSUSA/10405 /201607	Periodic Safety Update EU Single assessment - evolocumab	09/02/2017	n/a		PRAC Recommendation - maintenance
IA/0013	A.7 - Administrative change - Deletion of manufacturing sites	16/12/2016	n/a		
II/0012	Variation B.II.G.2 B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	15/12/2016	n/a		The applicant has submitted a Type II variation to the marketing authorization for Repatha (evolocumab) to gain approval of a Post Approval Change Management Protocol (PACMP) for the introduction of Building PM3 in Amgen Technology Ireland (ADL) Dun Laoghaire, Co. Dublin, Ireland (hereafter referred to as ADL-PM3) as an additional (alternative), drug product manufacturing site for the formulation and aseptic filling of Repatha (evolocumab) syringes. The currently licensed Amgen drug product manufacturing facilities are Amgen Manufacturing Limited, Building 1 (JU001, also known as AML-1) and Building 14 (JU014, also known as AML-14), in Juncos, Puerto Rico. Addition of ADL-PM3 is intended to increase the overall capacity and prevent points of failure in supply by diversifying manufacturing and product storage locations. The Marketing Authorisation Holder (MAH) provided a PACMP for the formulation and aseptic filling of Repatha syringes. The PACMP is considered acceptable. It contains an acceptable description of the change. The section on risk assessment does not cover the risk of oxidation, although this risk is sufficiently addressed under characterisation and in the appendix. For the remaining aspects, the risk assessment was sufficient. In addition, the PACMP

					describes the approaches which the MAH intends to apply for process comparison - including comparison of the facilities, the in process control strategy and process validation strategy – and product comparability – including release testing, characterisation and stability (accelerated conditions). In addition, post-change drug product lots will be put on stability per the established annual stability protocol and stored under recommended storage conditions (RSC) of 2°C to 8°C. The stability results at RSC to the 3 month time point will be submitted to the Agency in the Type IB variation to implement the change. The RSC studies will continue through expiry per the existing stability commitments (3.2.P.8.2, Post-approval Stability Protocol and Stability Commitment [140 mg/mL PFS]). One question was asked regarding comparability criteria and was adequately resolved by the MAH. Therefore the PACMP can be approved. The benefit-risk balance of Repatha in the approved indication remains positive.
IB/0010/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.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	05/10/2016	n/a		

IB/0009/G	This was an application for a group of variations. B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol	26/09/2016	17/02/2017	SmPC	
PSUSA/10405 /201601	Periodic Safety Update EU Single assessment - evolocumab	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0008	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/08/2016	n/a		
N/0007	Update of the instructions for use for the 140mg solution for injection in pre-filled pen and prefilled syringe. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/06/2016	17/02/2017	PL	
IB/0005/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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	16/03/2016	n/a		

	procedure				
IB/0003	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	08/01/2016	n/a		
IB/0004	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/12/2015	n/a		
IB/0001	B.IV.1.z - Change of a measuring or administration device - Other variation	18/09/2015	n/a		