Hemlibra

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
R/0032	Renewal of the marketing authorisation.	21/07/2022	15/09/2022	SmPC, Annex II and Labelling	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Hemlibra in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.

[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).

PSUSA/10668 /202111	Periodic Safety Update EU Single assessment - emicizumab	10/06/2022	n/a		PRAC Recommendation - maintenance
II/0029/G	This was an application for a group of variations. B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for 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.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	05/05/2022	15/09/2022	Annex II	The Annex IIA has been updated to add the following site as a manufacturer of the biological active substance: F. Hoffmann La Roche Ltd. Grenzacherstrasse 124 4070 Basel Switzerland
IB/0031	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	20/04/2022	n/a		
II/0028	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/03/2022	n/a		

II/0025	Update of sections 4.4, 4.8 and 5.1 of the Product information concerning immunogenicity and loss of efficacy due to anti-emicizumab antibodies. The RMP (v.4.1) is proposed to be updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/03/2022	15/09/2022	SmPC, Labelling and PL	Update of the Product Information and RMP to inform HCPs that unexpected bleeding symptoms while on emicizumab suggest the possibility of an antidrug antibody (with frequency uncommon). This is based on pooled data from 7 Phase III Clinical trials (BH29884, BH29992, BH30071, BO39182, YO39309, JO39881, and MO39129). For more information, please refer to the Summary of Product Characteristics.
II/0026	Update of section 4.8 of the SmPC to include new data related to hypersensitivity, in compliance with the PRAC recommendation following the assessment of PSUSA/00010668/202011. The PIL is updated in accordance with the changes to the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/10/2021	15/09/2022	SmPC and PL	The product information has been updated to include the following ADRs from postmarketing surveillance: Angioedema (uncommon), urticaria (common) and rash (common)
II/0023/G	This was an application for a group of variations. 1. B.I.a.1.g (Type II) - To add Chugai Pharma Manufacturing Co, Ltd, 5-1, Ukima 5-Chrome, Kita-Ku-Tokyo 115-8543, Japan as an alternative site responsible for the manufacturing, testing and storage of the active substance emicizumab. 2. B.I.a.1.f (Type IB) - To add BioReliance Ltd, Todd Campus, West of Scotland Science Park, Glasgow, G20 OXA UK as an alternative in-process control (IPC) testing site responsible for the mycoplasma	16/09/2021	n/a		

	testing of the preharvest cell culture fluid (PHCCF). 3. B.I.a.1.f (Type IB) - To add Chugai Pharma Manufacturing, Co., Ltd. 116-3, Kiyohara Kogyodanchi, Utsunomiya City, Tochigi 321-3231 Japan (UT) as an alternative in-process control (IPC) testing site responsible for the mycoplasma testing of the preharvest cell culture fluid (PHCCF). 4. B.I.a.1.f (Type IB) - To add Charles River Laboratories, Inc. 466 Devon Park Drive, Wayne, PA 19406 USA as an alternative in-process control (IPC) testing site responsible for the virus testing of the preharvest cell culture fluid (PHCCF). 5. B.I.a.3.a (Type IB) - To increase the batch size of the active substance emicizumab manufactured at Chugai Ukima Building W40, Japan from 2000 L to 6000 L. 6. B.I.a.4.c (Type IB) - To delete the non-significant in-process test for Leptospira applied during the manufacture of the active substance emicizumab at Chugai Ukima Building W40, Japan. 7. B.I.c.1.c (Type IB) - Change in the quantitative composition of the immediate packaging of the active substance emicizumab. In addition, the Marketing Authorisation Holder (MAH) has taken the opportunity to update sections of Module 3.				

	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier 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.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.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.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile)				

N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2021	15/09/2022	PL	
II/0021	Submission of an updated RMP version 2.6 in order to add thromboembolic events without concomitant aPCC as an important potential risk in the safety specifications and to update the milestones for BO40853/SURVEY study following approval of the protocol v3 (via MEA PRO 002.2). 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	08/07/2021	n/a		
PSUSA/10668 /202011	Periodic Safety Update EU Single assessment - emicizumab	10/06/2021	n/a		PRAC Recommendation - maintenance
PSUSA/10668 /202005	Periodic Safety Update EU Single assessment - emicizumab	14/01/2021	n/a		PRAC Recommendation - maintenance
IB/0020	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	07/12/2020	18/08/2021	SmPC	
IB/0017	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	19/08/2020	18/08/2021	SmPC and PL	

IB/0018	B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation	28/07/2020	n/a		
PSUSA/10668 /201911	Periodic Safety Update EU Single assessment - emicizumab	11/06/2020	n/a		PRAC Recommendation - maintenance
IB/0015	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/12/2019	23/01/2020	SmPC	
PSUSA/10668 /201905	Periodic Safety Update EU Single assessment - emicizumab	28/11/2019	n/a		PRAC Recommendation - maintenance
IB/0013/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	09/07/2019	n/a		
IB/0012/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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	21/06/2019	n/a		

PSUSA/10668 /201811	Periodic Safety Update EU Single assessment - emicizumab	14/06/2019	n/a		PRAC Recommendation - maintenance
IB/0011	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	11/04/2019	23/01/2020	SmPC	
II/0002	Extension of Indication to include routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII<1 %) without FVIII activity; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information of the pivotal trials. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor corrections and clarity to sections 4.4, 4.5 and 4.6 of the SmPC. 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, Labelling and PL	Please refer to Scientific Discussion Hemlibra-H-C-4406-II-02
PSUSA/10668 /201805	Periodic Safety Update EU Single assessment - emicizumab	13/12/2018	14/02/2019	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10668/201805.
IB/0008	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	25/10/2018	n/a		

IB/0007	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	22/10/2018	14/02/2019	SmPC	
IB/0005	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	23/08/2018	14/02/2019	SmPC, Labelling and PL	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	14/02/2019	PL	
IB/0003/G	This was an application for a group of variations. B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	07/06/2018	n/a		
T/0001	Transfer of Marketing Authorisation	16/04/2018	30/04/2018	SmPC, Labelling and PL	