Cablivi

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/0050	Update of section 4.2 of the SmPC in order to include further administration instructions in case the first intravenous dose of caplacizumab is missed and plasma exchange is already administered, based on final results from study ALX0681-C103; this is a Phase 1, single-center, randomized, double-blind,	17/10/2024	22/11/2024	SmPC and PL	SmPC new text: In section 4.2 under Missed dose the following text is added: "The first dose of caplacizumab should be administered intravenously before the initial plasma exchange. If the

[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).

	placebo controlled, 2 part study that evaluated the safety, tolerability, PK/PD profile, and immunogenicity of single IV and SC doses (Part I) or multiple SC doses once daily for 7 days (Part II) of caplacizumab in Japanese and White healthy volunteers. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				administration of the first intravenous dose of caplacizumab is missed and plasma exchange is already administered, the first caplacizumab dose should still be administered intravenously after the plasma exchange is complete and the next dose should be administered subcutaneously on the following day according to the usual dosing schedule". For more information, please refer to the Summary of Product Characteristics.
II/0052	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	07/11/2024	n/a		
IB/0051/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	25/10/2024	n/a		

II/0049/G	This was an application for a group of variations. B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits B.I.b.1.i - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Where there is no monograph in the European/National Ph. for the AS, a change in specification from in-house to a non-official/third country Ph. 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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	04/07/2024	n/a		
PSUSA/10713 /202308	Periodic Safety Update EU Single assessment - caplacizumab	11/04/2024	n/a		PRAC Recommendation - maintenance
II/0047/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters	08/02/2024	n/a		

	and/or limits of the finished product - Tightening of specification limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test 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 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.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number 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 B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - 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				

IB/0044	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	02/05/2023	n/a		
IA/0045	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/04/2023	n/a		
R/0042	Renewal of the marketing authorisation.	23/02/2023	17/04/2023	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Cablivi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. The PI is brought in line with the latest QRD template. The statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.
PSUSA/10713 /202208	Periodic Safety Update EU Single assessment - caplacizumab	16/03/2023	n/a		PRAC Recommendation - maintenance
II/0040	Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC in order to update information on long-term efficacy and safety based on final results from study ALX0681-C302/LTS16371 - Prospective Follow-up Study for Patients who Completed Study ALX0681-C301 (HERCULES) to Evaluate Long-term Safety and Efficacy of Caplacizumab (Post-HERCULES), listed as a category 3 study in the RMP. The Post-HERCULES	12/01/2023	17/04/2023	SmPC	SmPC new text Section 4.4 Thrombolytic drugs such as urokinase, tissue plasminogen activator (t-PA) (e.g. alteplase) are added as increasing the risk of bleeding with concomitant use with Cablivi Section 4.5 It is added that no interaction studies evaluating use of caplacizumab with Antiplatelet agents, thrombolytic drugs

	study was a Phase III, 36-month follow-up study from HERCULES (parent study) to evaluate the long-term outcomes as well as the safety and efficacy of repeat use of caplacizumab in patients who experienced a recurrence of aTTP. The RMP version 3.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				such as urokinase, tPA (e.g. alteplase) have been performed. Section 5.1 Results of study Study ALX0681-C302 (Post-HERCULES) are reported.
IA/0041/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.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	20/09/2022	n/a		
IA/0039/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	14/09/2022	n/a		

	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				
IA/0038/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	14/09/2022	n/a		
II/0035	Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on increased risk of bleeding based on a safety evaluation report; the Package Leaflet is updated accordingly. The RMP version 2.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/06/2022	12/12/2022	SmPC and PL	SmPC new text 4.4 Special warnings and precautions for use Bleeding Cablivi increases the risk of bleeding. Cases of major bleeding, including life-threatening and fatal bleeding have been reported in patients receiving caplacizumab, mainly in those using concomitant anti-platelet agents or anticoagulants. Caplacizumab should be used with caution in patients with underlying conditions that may predispose them to a higher risk of bleeding In case of clinically significant bleeding, treatment with Cablivi should be interrupted. If needed, the use of von Willebrand Factor concentrate could be considered to correct hemostasis. Cablivi should only be restarted upon the advice of a physician experienced in the management of thrombotic microangiopathies. If Cablivi is restarted, monitor closely for signs of bleeding. In the setting of concomitant use of oral anticoagulants,

					anti-platelet agents or heparin The risk of bleeding is increased with concomitant use of Cablivi with drugs affecting hemostasis and coagulation. Initiation or continuation of treatment with oral anticoagulants (e.g., vitamin K antagonists or direct oral anticoagulants [DOAC] such as thrombin inhibitors or factor Xa inhibitors), anti-platelet agents or heparin requires a careful consideration and close clinical monitoring. In patients with coagulopathies Due to a potential increased risk of bleeding, use of Cablivi in patients with underlying coagulopathies (e.g. hemophilia, other coagulation factor deficiencies) must be accompanied by close clinical monitoring. In patients undergoing surgery If a patient is to undergo elective surgery, an invasive dental procedure or other invasive interventions, the patient must be advised to inform the physician or dentist that they are using caplacizumab and it is recommended to withhold treatment for at least 7 days before the planned intervention. The patient must also notify the physician who supervises the treatment with caplacizumab about the planned procedure. After the risk of surgical bleeding has resolved, and caplacizumab is resumed, the patient should be monitored closely for signs of bleeding. If emergency surgery is needed, the use of von Willebrand Factor concentrate is recommended to correct hemostasis. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10713 /202108	Periodic Safety Update EU Single assessment - caplacizumab	07/04/2022	n/a		PRAC Recommendation - maintenance

IB/0037	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/12/2021	n/a		
IB/0034	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	25/11/2021	12/12/2022	SmPC	
PSUSA/10713 /202102	Periodic Safety Update EU Single assessment - caplacizumab	30/09/2021	n/a		PRAC Recommendation - maintenance
IB/0032	B.II.e.z - Change in container closure system of the Finished Product - Other variation	02/06/2021	n/a		
PSUSA/10713 /202008	Periodic Safety Update EU Single assessment - caplacizumab	09/04/2021	n/a		PRAC Recommendation - maintenance
IB/0031	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	04/03/2021	n/a		
IB/0030	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	04/03/2021	n/a		
IA/0029/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	07/12/2020	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/10/2020	12/12/2022	PL	
IB/0026	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	09/10/2020	n/a		
PSUSA/10713 /202002	Periodic Safety Update EU Single assessment - caplacizumab	01/10/2020	n/a		PRAC Recommendation - maintenance
IB/0025	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/07/2020	n/a		
IA/0023	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	15/07/2020	n/a		
IA/0024	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	13/07/2020	n/a		
II/0021	Extension of indication to include adolescents weighing over 40 kg in the authorised indication for Cablivi; as a consequence, sections 4.1, 4.2, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is	30/04/2020	09/06/2020	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0021'

	brought in line with the latest QRD template version. The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10713 /201908	Periodic Safety Update EU Single assessment - caplacizumab	12/03/2020	n/a		PRAC Recommendation - maintenance
IA/0018/G	This was an application for a group of variations. 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.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	25/11/2019	n/a		
IA/0019	B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	22/11/2019	n/a		
IB/0017	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	22/11/2019	n/a		
IB/0015/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	20/11/2019	n/a		

	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.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				
IA/0016	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	25/10/2019	n/a		
IA/0014	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/10/2019	n/a		
PSUSA/10713 /201902	Periodic Safety Update EU Single assessment - caplacizumab	03/10/2019	n/a		PRAC Recommendation - maintenance
IB/0013	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/08/2019	n/a		
IA/0012	B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	26/07/2019	n/a		

IB/0011	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/07/2019	n/a		
IB/0009	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	06/06/2019	n/a		
IA/0008	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	16/05/2019	n/a		
IA/0007	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	26/04/2019	n/a		
IA/0006/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/04/2019	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				
IA/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	21/03/2019	n/a		
IAIN/0003	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	12/02/2019	08/10/2019	SmPC, Labelling and PL	
IB/0002	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	05/11/2018	n/a		
IB/0001	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	22/10/2018	08/10/2019	SmPC, Labelling and PL	