Ceplene

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
T/0043	Transfer of Marketing Authorisation	31/08/2022	09/09/2022	SmPC, Labelling and PL	
S/0042	11th annual re-assessment	25/03/2021	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data

[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).

					submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Ceplene should be maintained.
PSUSA/1610/202004	Periodic Safety Update EU Single assessment - histamine (indicated for acute myeloid leukemia)	29/10/2020	n/a		PRAC Recommendation - maintenance
II/0040	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	29/10/2020	n/a		
S/0039	Annual re-assessment.	12/12/2019	n/a		
PSUSA/1610/201904	Periodic Safety Update EU Single assessment - histamine (indicated for acute myeloid leukemia)	31/10/2019	n/a		PRAC Recommendation - maintenance
PSUSA/1610/201804	Periodic Safety Update EU Single assessment - histamine (indicated for acute myeloid leukemia)	31/10/2018	n/a		PRAC Recommendation - maintenance
R/0036	Renewal of the marketing authorisation.	31/05/2018	26/07/2018	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 Ceplene in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
S/0035	9th annual re-assessment.	31/05/2018	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation

					under exceptional circumstances of Ceplene should be maintained.
II/0034	Submission of study report X-03064-3306- A cohort study to follow-up Minimal Residual Disease (MRD) in patients with Acute Myeloid Leukemia (AML) in First Complete Remission (CR1) - Comparison of patients who receive Ceplene/Interleukin-2 as remission maintenance therapy with matched controls - to fulfil SOB 002. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/05/2018	26/07/2018	Annex II	As part of a Type II variation application the MAH submitted the final study report of the Ceplene Cohort Study 3306. The CHMP considered that the 3306 Cohort study does not further contribute in a significant way to the understanding of the B/R of Ceplene/IL2 in the maintenance treatment of patients with acute myeloid leukaemia in first remission. However, based on the accumulated data so far, the overall benefit/risk balance of Ceplene in the approved indication remains unchanged. Based on the poor uptake of Ceplene/IL 2 and in light of the available efficacy data generated since the granting of the Marketing Authorisation, the CHMP agreed to close the remaining specific obligation in the Annex II (SOB 002). Due to the rarity of the disease, the data are still not as comprehensive as a full marketing authorisation. The MAH shall therefore continue to provide yearly updates on any new information concerning efficacy and safety of the product in patients with acute myeloid leukaemia in first complete remission concomitantly treated with interleukin-2 (IL-2) as a condition (specific obligation) to the marketing authorisation under exceptional circumstances.
T/0033	Transfer of Marketing Authorisation	17/11/2017	08/12/2017	SmPC, Labelling and PL	
PSUSA/1610/ 201704	Periodic Safety Update EU Single assessment - histamine (indicated for acute myeloid leukemia)	26/10/2017	n/a		PRAC Recommendation - maintenance

IA/0031/G	This was an application for a group of variations. 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.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	28/04/2017	n/a		
S/0030	8th Annual Re-assessment	23/03/2017	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Ceplene should be maintained.
IA/0029	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	07/11/2016	n/a		
PSUSA/1610/ 201604	Periodic Safety Update EU Single assessment - histamine (indicated for acute myeloid leukemia)	27/10/2016	n/a		PRAC Recommendation - maintenance
N/0028	Update of the package leaflet with revised contact details of the local representatives for Estonia, Italy, Spain, Poland and France. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/07/2016	08/12/2017	PL	

S/0026	7th Annual Re-assessment.	01/04/2016	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Ceplene should be maintained.
PSUSA/1610/ 201504	Periodic Safety Update EU Single assessment - histamine (indicated for acute myeloid leukemia)	06/11/2015	n/a		PRAC Recommendation - maintenance
II/0024	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/09/2015	n/a		
IB/0023/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products 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 B.II.b.2.a - Change to importer, batch release	22/06/2015	30/06/2016	Annex II and PL	

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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.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.z - Change to in-process tests or limits applied during the manufacture of the finished 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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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.3.z - Change in the manufacturing process of				

	the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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				
S/0022	6th Annual Re-assessment	26/03/2015	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Ceplene should be maintained.
PSUV/0021	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
S/0014	4th Annual Re-assessment.	23/01/2014	21/03/2014	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Ceplene should be varied. In addition, considering the outcome of the GCP inspection and available MRD data from study EPC2008-02, the CHMP considered that the specific obligation should be revised to: Evaluate Minimal Residual Disease (MRD) at baseline and follow-up in a clinical study or registry, as appropriate, for the assessment of the anti-leukaemic activity of Ceplene plus low dose Interleukin-2 in a sufficient number of adult patients stratified by age greater or less than 60 years with Acute Myeloid Leukemia in First Complete Remission.

S/0020	5th Annual Re-assessment.	20/03/2014	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
II/0017	Update of section 4.8 of the SmPC to include leucopenia, neutropenia, upper respiratory tract infection, gastritis and abdominal distension as new adverse drug reactions based on safety data from study EPC2008-02. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and revise the labelling of the outer carton in line with QRD review of the specimen. The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	06/02/2015	SmPC, Labelling and PL	Based on the safety information available from study EPC2008-02, an open-label, multicentre study of the effects of remission maintenance therapy with Ceplene in conjunction with low-dose IL-2 on immune response and Minimal Residual Disease (MRD) in adult patients with AML in first Complete Remission (CR1), the CHMP considered appropriate to include leucopenia, neutropenia, upper respiratory tract infection, pneumonia, gastritis and abdominal distension as new adverse drug reactions in the product information of Ceplene. The benefit risk balance of Ceplene remains positive.
PSUV/0019	Periodic Safety Update	07/11/2013	n/a		PRAC Recommendation - maintenance
R/0015	Renewal of the marketing authorisation.	27/06/2013	26/08/2013	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers by consensus that the risk-benefit balance of Ceplene in the treatment of relapse prevention in adult patients with acute myeloid leukaemia in first complete remission in

					combination with interleukin-2 remains favourable and therefore recommends the renewal of the marketing authorisation under exceptional circumstances. The CHMP also recommends that one additional five-year renewal be required based on the limited number of patients exposed to Ceplene outside of clinical trials which precludes the adequate collection of pharmacovigilance data in real-world clinical use.
IG/0277	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/03/2013	n/a		
T/0013	MA Transfer from EpiCept to MEDA AB Transfer of Marketing Authorisation	24/09/2012	15/10/2012	SmPC, Labelling and PL	
A20/0011	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).	15/03/2012	31/05/2012		Please refer to the assessment report: EMEA/H/C/796/A-20/0011
S/0012	Annual re-assessment.	16/02/2012	20/04/2012	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the

					product remains favourable.
S/0010	Annual re-assessment.	17/02/2011	14/04/2011	Annex II	
II/0006	Update of SPC sections 4.2, 6.4 and 6.6 and PL sections 3 and 5 with a description of how to prepare, dispense, and store interleukin-II, when used in conjuction with Ceplene. Update of Summary of Product Characteristics and Package Leaflet	16/12/2010	24/01/2011	SmPC and PL	
IA/0008/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition 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	09/11/2010	n/a		
IB/0007	To change the bulk hold time from 30 to 48 hours B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	02/06/2010	n/a		
S/0005	1st annual re-assessment	18/02/2010	29/04/2010	Annex II	The CHMP having reviewed the evidence of compliance with the Specific Obligations submitted by the Marketing Authorisation Holder and having re-assessed the

					benefit/risk profile of the medicinal product, recommended that no amendment to the Annexes I and III of the Commission Decision is necessary and that the Marketing Authorisation remains under Exceptional Circumstances. Annex II.C has been amended according to the conclusions reached during CHMP discussion
IB/0003	IB_33_Minor change in the manufacture of the finished product	19/08/2009	n/a		
IA/0002	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	17/12/2008	n/a		
IA/0001	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	21/11/2008	n/a		