Cotellic

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/1730	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/03/2024		SmPC and PL	
II/0027	Update of sections 4.4 and 5.1 of the SmPC in order to update information based on final results from study ML39302 listed as a category 3 study in the	12/01/2023	28/04/2023	SmPC	SmPC new text Limited data show that the safety of the combination of Cotellic and vemurafenib in patients with a BRAF V600

[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).

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	RMP in order to fulfil MEA/003.5; this is a non-interventional PASS study to investigate the effectiveness, safety and utilization of cobimetinib and vemurafenib in patients with and without brain metastasis with BRAF V600 mutant melanoma under real world conditions. The RMP version 5.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				mutation-positive melanoma which has metastasised to the brain is consistent with the known safety profile of Cotellic in combination with vemurafenib. The efficacy of the Cotellic and vemurafenib combination in these patients has not been evaluated. The intracranial activity of Cotellic is unknown. For more information, please refer to the Summary of Product Characteristics.
II/0028	Please refer to the Recommendations section above C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/11/2022	28/04/2023	SmPC and PL	Not applicable
II/0025	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on final results from study GO29665 (iMATRIX_cobimetinib) which corresponds to Study 4 of PIP P/0119/2021. This is a phase I/II, multicentre, open-label, dose-escalation study of the safety, efficacy and pharmacokinetics of cobimetinib in paediatric and young adult patients with previously treated solid tumours. The section 2 of 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	19/05/2022	28/04/2023	SmPC and PL	SmPC new text The safety of Cotellic in children and adolescents has not been fully established. The safety of Cotellic was assessed in a multi-centre, open-label, dose-escalation study in 55 paediatric patients aged 2 to 17 years with solid tumours. The safety profile of Cotellic in these patients was consistent with that in the adult population. Currently available data are described in sections 4.8, 5.1 and 5.2 of the SmPC, but no recommendation on posology can be made. For more information, please refer to the Summary of Product Characteristics.

IA/0026	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)	01/03/2022	n/a		
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/11/2021	10/02/2022	PL	
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2021	10/02/2022	PL	
IB/0022/G	This was an application for a group of variations. B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure 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.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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	30/06/2021	n/a		

	control/testing takes place B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
PSUSA/10450 /202008	Periodic Safety Update EU Single assessment - cobimetinib	11/03/2021	n/a		PRAC Recommendation - maintenance
IA/0021	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	12/02/2021	10/02/2022	SmPC	
R/0019	Renewal of the marketing authorisation.	30/04/2020	25/06/2020	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Cotellic in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10450 /201908	Periodic Safety Update EU Single assessment - cobimetinib	12/03/2020	n/a		PRAC Recommendation - maintenance
IB/0017	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	09/08/2019	25/06/2020	SmPC	
II/0016	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	11/07/2019	n/a		

PSUSA/10450 /201808	Periodic Safety Update EU Single assessment - cobimetinib	14/03/2019	n/a		PRAC Recommendation - maintenance
IA/0015	A.7 - Administrative change - Deletion of manufacturing sites	26/02/2019	n/a		
PSUSA/10450 /201802	Periodic Safety Update EU Single assessment - cobimetinib	06/09/2018	n/a		PRAC Recommendation - maintenance
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	25/06/2020	PL	
T/0011	Transfer of Marketing Authorisation	20/02/2018	16/03/2018	SmPC, Labelling and PL	
PSUSA/10450 /201708	Periodic Safety Update EU Single assessment - cobimetinib	08/03/2018	n/a		PRAC Recommendation - maintenance
IG/0887	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)	29/01/2018	n/a		
PSUSA/10450 /201702	Periodic Safety Update EU Single assessment - cobimetinib	28/09/2017	n/a		PRAC Recommendation - maintenance
PSUSA/10450 /201608	Periodic Safety Update EU Single assessment - cobimetinib	23/03/2017	24/05/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10450/201608.

PSUSA/10450 /201602	Periodic Safety Update EU Single assessment - cobimetinib	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0006/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.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 variation	19/07/2016	24/05/2017	SmPC	
II/0004/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and efficacy results of studies GO28141 and NO25395. The RMP has been updated accordingly (version 2.1). In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor amendments in sections 5.1 and 5.3 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2016	24/05/2017	SmPC	At the initial Marketing Authorisation Application, the overall survival data from the pivotal phase III Study GO28141 ("coBRIM") were immature. In the present variation, an update of overall survival and safety was provided for Study GO28141, and updated efficacy analyses were provided for the supportive phase 1b Study NO25395 ("BRIM7"). The SmPC has been updated with the updated efficacy results from both studies. The survival benefit of the addition of cobimetinib to vemurafenib in the treatment of unresectable or metastatic malignant melanoma has now been established to be approximately 5 months in median. Small changes in the cumulative frequencies of adverse drug reactions were observed in the Study GO28141 safety update with 10 month's increased median follow-up. No changes were made to the SmPC with regard to safety. The

					currently presented ADR frequencies correspond to the median duration of treatment.
II/0001/G	This was an application for a group of variations. Update of sections 4.2, 4.8 and 5.2 of the SmPC to reflect the results GP29342 with recommendations for patients with hepatic impairment. Furthermore, the MAH submitted results of the in vitro CYP time-dependent inhibition study (15-1983). In addition, the MAH took the opportunity to use the term CYP3A throughout the SmPC to cover both CYP3A4 and CYP3A5, in line with previous recommendations, and to bring the product in line with the latest QRD template. The Package Leaflet was updated accordingly. The Risk Management Plan was updated to reflect the completion of the studies. 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	28/04/2016	01/06/2016	SmPC, Labelling and PL	The pharmacokinetics and safety of Cotellic (cobimetinib) in subjects with mild, moderate or severe hepatic impairment compared to healthy subjects was evaluated with study GP29342. Systemic total cobimetinib exposures after a single dose were similar in subjects with mild or moderate hepatic impairment compared to healthy subjects, while subjects with severe hepatic impairment had lower total cobimetinib exposures (AUC0-∞ geometric mean ratio of 0.69 compared to healthy subjects) which is not considered to be clinically significant. Unbound cobimetinib exposures were similar between subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function while subjects with severe hepatic impairment had approximately 2-fold higher exposures. No dose adjustment is therefore recommended in patients with hepatic impairment. Patients with severe hepatic impairment may have increased plasma concentrations of unbound cobimetinib compared to patients with normal hepatic function. Liver laboratory abnormalities can occur with Cotellic and caution should be used in patients with any degree of hepatic impairment.
II/0003	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/05/2016	24/05/2017	SmPC and PL	
IA/0002	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	04/01/2016	01/06/2016	SmPC	