CABOMETYX

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/0040	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/06/2025	23/07/2025	SmPC and PL	Please refer to Scientific Discussion 'Cabometyx-H-C-4163-II-0040'.
IA/0039/G	This was an application for a group of variations.	05/04/2024	n/a		

[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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	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 B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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				
IB/0038	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	27/11/2023	n/a		
IB/0037	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/10/2023	19/09/2024	SmPC and PL	
II/0033	Submission of the final report from study F-FR-60000-001 (CASSIOPE) listed as a category 3 study in the RMP. This is a prospective, non-imposed and non-interventional study of cabozantinib tablets in adults with advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy. The RMP version 7.0 has also been submitted.	28/09/2023	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0036	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	27/06/2023	n/a		
IB/0035	C.I.3.z - 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 - Other variation	19/06/2023	04/10/2023	SmPC	
II/0032	Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on Vanishing Bile Duct Syndrome (VBDS), to add embolism arterial to the list of adverse drug reactions (ADRs) with frequency Uncommon and to add vanishing bile duct syndrome to the list of adverse drug reactions (ADRs) with frequency Not known based on the cumulative review of the global safety database and literature search. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/06/2023	04/10/2023	SmPC and PL	Based on safety data collected in the post-marketing setting, section 4.4 of the SmPC has been updated to add VBDS as a new warning and section 4.8 has been updated to add embolism arterial with frequency Uncommon and VBDS with frequency Not known to the list of ADRs.

IA/0031/G	This was an application for a group of variations. 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 B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	10/01/2023	n/a		
IA/0030/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.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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/10/2022	n/a		

PSUSA/10180 /202111	Periodic Safety Update EU Single assessment - cabozantinib	21/07/2022	29/09/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10180/202111.
II/0029	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	15/09/2022	04/10/2023	SmPC and PL	SmPC sections 4.4 and 4.8 have been updated as follows: In differentiated thyroid carcinoma, dose reductions and dose interruptions occurred in 67% and 71% respectively of cabozantinib treated patients in the clinical trial (COSMIC-311). Two dose reductions were required in 33% of patients. The median time to first dose reduction was 57 days and to first dose interruption was 38.5 days. The most common serious adverse drug reactions in the DTC population (≥1% incidence) are diarrhoea, pleural effusion, pneumonia, pulmonary embolism, hypertension, anaemia, deep vein thrombosis, hypocalcemia, osteonecrosis of jaw, pain, palmar-plantar erythrodysaesthesia syndrome, vomiting and renal impairment. The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the DTC population included diarrhoea, PPES, hypertension, fatigue, decreased appetite, nausea, alanine aminotransferase increased, aspartate aminotransferase increased and hypocalcaemia. For more information, please refer to the Summary of Product Characteristics.

II/0023	Extension of indication to include monotherapy treatment of adults and adolescent patients aged 12 years and older, with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy for CABOMETYX; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The MAH also took the opportunity to update the local representative for Spain. Version 6.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/03/2022	29/04/2022	SmPC and PL	Please refer to Scientific Discussion 'Cabometyx-H-C-004163/II/0023
IB/0027	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	29/12/2021	n/a		
IB/0025	C.I.3.z - 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 - Other variation	09/11/2021	29/04/2022	SmPC	
IA/0026	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	19/10/2021	29/04/2022	SmPC	
WS/2104	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	02/09/2021	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites				
IA/0024	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	10/08/2021	n/a		
IB/0021	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)	25/06/2021	29/04/2022	SmPC and PL	
R/0018	Renewal of the marketing authorisation.	25/02/2021	21/04/2021	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 CABOMETYX in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity
II/0017	Extension of indication to include in combination with nivolumab first line treatment of advanced renal cell carcinoma for CABOMETYX; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/02/2021	26/03/2021	SmPC and PL	Please refer to Scientific Discussion 'Cabometyx-H-C-4163-II-0017'
IB/0020	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	26/02/2021	n/a		

	procedure				
IB/0019	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	26/02/2021	n/a		
IB/0016/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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.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.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.b.1.z - Change in the specification parameters	22/10/2020	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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				
IB/0015/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.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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 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	22/10/2020	26/03/2021	Annex II and PL	

	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 B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing 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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation				
IA/0014	B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	05/06/2020	31/07/2020	SmPC, Labelling and PL	

II/0012	Update of section 4.4 of the SmPC to include the risk of Osteonecrosis as a warning. Update of Section 4.8 of the SmPC based on the Company Core Safety Information: - to add Dysphagia and Hyperkeratosis to the existing ADR, - to replace Peripheral sensory neuropathy by Peripheral neuropathy in order to reflect the broader medical concept and to add DVT (Deep vein thrombosis) to the existing ADR venous thrombosis in order to alert prescribers to the most frequently reported type of venous thrombosis. Changes to the frequency categorisation of some ADRs are also proposed based on new pooled data. Additionally, an update of section 4.2 of the SmPC to align the SmPC of other cabozantinib medicinal product is included. The Package Leaflet is updated accordingly. The MAH took the opportunity to align the product Information with the QRDv10.1 and update the local representative information of Hungary C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/04/2020	31/07/2020	SmPC, Labelling and PL	CABOMETYX (cabozantinib) tablets and COMETRIQ (cabozantinib) capsules are not bioequivalent and should not be used interchangeably. For RCC and HCC, the recommended dose of CABOMETYX is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction of CABOMETYX therapy. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose. Osteonecrosis: Events of osteonecrosis of the jaw (ONJ) have been observed with cabozantinib. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy. Patients should be advised regarding oral hygiene practice. Cabozantinib treatment should be held at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ. The most common serious adverse drug reactions in the RCC population (≥1% incidence) are abdominal pain,

					diarrhoea, nausea, hypertension, embolism, hyponatraemia, pulmonary embolism, vomiting, dehydration, fatigue, asthenia, decreased appetite, deep vein thrombosis, dizziness, hypomagnesaemia and palmar-plantar erythrodysaesthesia syndrome (PPES). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the RCC population included diarrhoea, fatigue, nausea, decreased appetite, PPES, hypertension, weight decreased, vomiting, dysgeusia, constipation, and AST increased. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%). The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, asthenia, fatigue, PPES, diarrhoea, hyponatraemia, vomiting, abdominal pain and thrombocytopenia. The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, decreased appetite, PPES, fatigue, nausea, hypertension and vomiting.
IA/0013	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	06/03/2020	n/a		

N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2019	31/07/2020	PL	
IAIN/0011	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/10/2019	31/07/2020	SmPC and PL	
IAIN/0009/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.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	19/08/2019	31/07/2020	Annex II and PL	
IA/0008	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	16/07/2019	n/a		
PSUSA/10180 /201811	Periodic Safety Update EU Single assessment - cabozantinib	27/06/2019	27/06/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10180/201811.
IA/0007	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	21/03/2019	n/a		
II/0005	Extension of indication to add Cabometyx as monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been	20/09/2018	12/11/2018	SmPC and PL	Please refer to the scientific discussion Cabometyx EMEA/H/C/004163/II/0005.

	treated with sorafenib; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated with safety and efficacy information. The package leaflet and the risk management plan (version 4.2) are updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10180 /201711	Periodic Safety Update EU Single assessment - cabozantinib	28/06/2018	23/08/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10180/201711.
II/0003	Extension of indication to include for the treatment of advanced renal cell carcinoma the 'treatment-naïve adults with intermediate or poor risk' for CABOMETYX; as a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The package Leaflet and risk management plan (version 3.2) are also updated accordingly. In addition, the marketing authorisation holder took the opportunity to make some editorial changes in the product information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/03/2018	08/05/2018	SmPC and PL	Please refer to Scientific Discussion CABOMETYX - EMEA/H/C/004163/II/0003
II/0002/G	This was an application for a group of variations. 1) C.I.4 (type II) Update of section 5.1 of the SmPC to reflect the final	09/11/2017	08/05/2018	SmPC and Annex II	Non-clinical and clinical information have been updated in the product information of Cabometyx: The carcinogenic potential of cabozantinib has been

	study results from clinical study XL184-308: A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy, to fulfil the condition to the marketing authorisation listed as a PAES in the Annex II. The RMP version 2.0 has also been submitted. 2) C.I.4 (type II) Update of section 5.3 of the SmPC to reflect the final study results from non-clinical study XL184-NC-036: 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Cabozantinib (XL184) in Rats. The RMP version 2.0 has also been submitted. 3) C.I.3.z (type IB) Update of section 4.5 of the SmPC to implement the wording agreed by the PRAC following the outcome of the PSUR procedure EMEA/H/C/PSUSA/10180/201603. In addition, the MAH took the opportunity to update the list of local representatives. C.I.3.z - 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 - Other variation 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				evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study XL184-NC-036, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes at exposures well below the intended exposure in humans. The clinical relevance of the observed neoplastic lesions in rats is uncertain. A statistically significant improvement in progression free survival (PFS) was demonstrated for Cabometyx compared to everolimus. A planned interim analysis of overall survival (OS) was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (202 events, HR=0.68 [0.51, 0.90], p=0.006). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomized to CABOMETYX as compared with everolimus (320 events, median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003). Comparable results for OS were observed with a follow-up analysis (descriptive) at 430 events. By submitting the final results of the post-authorisation efficacy study XL184-308 the MAH fulfils the Annex II condition imposed at time of initial marketing authorisation. The information regarding the effect of cabozantinib on other medicinal products is updated to reflect that because of high plasma protein binding levels of cabozantinib a plasma protein displacement interaction with warfarin may

					be possible. In case of such combination, INR values should be monitored.
PSUSA/10180 /201611	Periodic Safety Update EU Single assessment - cabozantinib	09/06/2017	n/a		PRAC Recommendation - maintenance