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/0005	Extension of indication to add Cabometyx as monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been 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.	20/09/2018	12/11/2018	SmPC and PL	Please refer to the scientific discussion Cabometyx EMEA/H/C/004163/II/0005.

[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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	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 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	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 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

	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				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