Cometriq

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/0053	Update of section 4.8 of the SmPC in order to add embolism arterial to the list of adverse drug reactions (ADRs) with frequency Uncommon based on literature search. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives	14/09/2023		SmPC and PL	Based on safety data collected in the post-marketing setting, section 4.8 of the SmPC has been updated to add embolism arterial with frequency Uncommon to the list of ADRs.

[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).

	in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0054/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.II.c.3.a.1 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or	06/06/2023	n/a		

	reagents NOT used in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.3 - Submission of a new/updated or				

	deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
IA/0055	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	01/06/2023	n/a		
IA/0052/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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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/0051/G	This was an application for a group of variations. 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/12/2022	n/a		
PSUSA/10180 /202111	Periodic Safety Update EU Single assessment - cabozantinib	21/07/2022	26/09/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10180/202111.
II/0049	Update of sections 4.4 and 4.8 of the SmPC in order to amend an existing warning on hypertension and add hypertensive crisis to the list of adverse drug reactions (ADRs) with frequency not known based on literature review and post-marketing and clinical data. The Package Leaflet is updated accordingly. 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	31/03/2022	26/09/2022	SmPC and PL	SmPC new text Hypertension, including hypertensive crisis, has been observed with cabozantinib. Blood pressure should be well-controlled prior to initiating cabozantinib. After cabozantinib initiation blood pressure should be monitored early and regularly and treated as needed with appropriate anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib treatment should be interrupted until blood pressure is controlled, after which cabozantinib can be resumed at a reduced dose. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued.

					For more information, please refer to the Summary of Product Characteristics.
IB/0048	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	16/12/2021	n/a		
II/0044	Update of section 5.1 of the SmPC based on the final results from study XL184-401 (EXAMINER) (SOB 001), a randomised, double-blind study to evaluate the efficacy and safety of cabozantinib (XL184) at 60 mg/day compared to a 140 mg/day in progressive, metastatic medullary thyroid cancer patients and as a consequence update of annex II in order to delete SOB 001. With the fulfilment of SOB 001 the MAH is requesting for the Cometriq MA to no longer be subject to specific obligations. The package leaflet is updated accordingly. The updated RMP version 5.5 has also been submitted. Furthermore, information on hepatotoxicity has been added to the section 4.4 and the cross reference between sections 4.1 and 4.4 has been removed for consistency. 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	22/07/2021	16/09/2021	SmPC, Annex II, Labelling and PL	Update of section 5.1 of the SmPC based on the final results from study XL184-401 (EXAMINER) (SOB 001), a randomised, double-blind study to evaluate the efficacy and safety of cabozantinib (XL184) at 60 mg/day compared to a 140 mg/day in progressive, metastatic medullary thyroid cancer patients and as a consequence update of annex II in order to delete SOB 001. With the fulfilment of SOB 001 the MAH is requesting for the Cometriq MA to no longer be subject to specific obligations. The package leaflet is updated accordingly. The updated RMP version 5.5 has also been submitted. Furthermore, information on hepatotoxicity has been added to the section 4.4 and the cross reference between sections 4.1 and 4.4 has been removed for consistency.

WS/2104	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.7 - Administrative change - Deletion of manufacturing sites	02/09/2021	n/a		
IA/0047/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	09/08/2021	n/a		
IAIN/0045/G	This was an application for a group of variations. 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.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol 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) 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	17/05/2021	12/08/2021	Annex II and PL	

	control/testing takes place B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IA/0043/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.6 - Administrative change - Change in ATC Code/ATC Vet Code	04/03/2021	12/08/2021	SmPC, Annex II and PL	
R/0042	Renewal of the marketing authorisation.	10/12/2020	11/02/2021	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Cometriq, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IA/0041/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	16/10/2020	n/a		

	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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0040/G	This was an application for a group of variations. 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	12/10/2020	n/a		
II/0036	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/07/2020	n/a		
IB/0039	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/06/2020	11/02/2021	Annex II	
II/0035	Update of section 4.2 to introduce a clarification in alignment with Cabometyx; update of section 4.4 of the SmPC to include the addition of the risk of	30/04/2020	11/02/2021	SmPC, Labelling and PL	COMETRIQ (cabozantinib) capsules and CABOMETYX (cabozantinib) tablets are not bioequivalent and should not be used interchangeably. The recommended dose of

	diarrhoea and additional text to the existing risks of thromboembolic events, haemorrhage, wound complications and Posterior reversible encephalopathy syndrome (PRES). Update of Section 4.8 of the SmPC, based on the Company Core Safety Information, 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. 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				COMETRIQ is 140 mg once daily, taken as one 80 mg orange capsule and three 20 mg grey capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. It should be expected that a majority of patients treated with COMETRIQ will require one or more dose adjustments (reduction and/or interruption) due to toxicity. Patients should therefore be closely monitored during the first eight weeks of therapy Events of venous thromboembolism, including pulmonary embolism and events of arterial thromboembolism, sometimes fatal, have been observed with cabozantinib. Cabozantinib should be used with caution in patients who are at risk for, or who have a history of, these events. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication. Severe haemorrhage, sometimes fatal, has been observed with cabozantinib. Patients who have evidence of involvement of the trachea or bronchi by tumour or a history of haemoptysis prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients with serious haemorrhage or recent haemoptysis. Diarrhoea, nausea/vomiting, decreased appetite, and stomatitis/oral pain were some of the most commonly reported GI adverse reactions. Prompt medical management, including supportive care with antiemetics, antidiarrhoeals, or antacids, should be instituted to prevent dehydration, electrolyte imbalances and weight loss. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or

					recurrent significant GI adverse reactions. Posterior reversible encephalopathy syndrome (PRES) has been observed with cabozantinib. PRES should be considered in any patient presenting with symptoms suggestive of the diagnosis, including seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with PRES.
II/0037	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	23/04/2020	n/a		
IA/0038	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		
R/0032	Renewal of the marketing authorisation.	12/12/2019	21/02/2020	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Cometriq, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2019	11/02/2021	PL	

IAIN/0034	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/10/2019	21/02/2020	SmPC and PL	
PSUSA/10180 /201811	Periodic Safety Update EU Single assessment - cabozantinib	27/06/2019	23/08/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10180/201811.
IAIN/0031/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 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.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 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	25/06/2019	23/08/2019	Annex II and PL	

R/0029	Renewal of the marketing authorisation.	31/01/2019	28/03/2019	SmPC and Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Cometriq, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. In this renewal, the CHMP agreed to postpone the due date of the Specific Obligation study, on grounds of the current rate of enrolment, as well as the anticipated time to achieve the required number of PFS events which has implications on the time needed until the primary endpoint can be analysed and results processed. It is therefore acceptable that the due date of the SOB is postponed till 30 September 2020.
PSUSA/10180 /201711	Periodic Safety Update EU Single assessment - cabozantinib	28/06/2018	27/08/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10180/201711.
R/0027	Renewal of the marketing authorisation.	09/11/2017	08/01/2018	Labelling	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Cometriq, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.

PSUSA/10180 /201611	Periodic Safety Update EU Single assessment - cabozantinib	09/06/2017	n/a		PRAC Recommendation - maintenance
IB/0026	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	25/04/2017	n/a		
II/0024	Update of section 5.3 of the SmPC to reflect the results of the final study report of the non-clinical study (XL184-NC-036) assessing the carcinogenicity potential in rat. In addition, the risk management plan (RMP) is being updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2017	08/01/2018	SmPC	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, 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 intend exposure in humans. The clinical relevance of the observed neoplastic lesions in rats is uncertain, but likely to be low.
R/0022	Renewal of the marketing authorisation.	10/11/2016	11/01/2017		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Cometriq, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
PSUSA/10180 /201603	Periodic Safety Update EU Single assessment - cabozantinib	13/10/2016	12/12/2016	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10180/201603.
T/0023	Marketing authorisation transfer from TMC Pharma Service Limited to Ipsen Pharma. Transfer of Marketing Authorisation	05/09/2016	30/09/2016	SmPC, Labelling and PL	
PSUSA/10180 /201509	Periodic Safety Update EU Single assessment - cabozantinib	14/04/2016	n/a		PRAC Recommendation - maintenance
R/0017	Renewal of the marketing authorisation.	19/11/2015	11/01/2016	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Cometriq, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
II/0018	Update of section 5.3 of the SmPC with the results from the carcinogenicity study in mice. Furthermore, the MAH took the opportunity to align the PI with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	30/09/2016	SmPC	In this variation the MAH updated the PI with the information that cabozantinib was not carcinogenic in the rasH2 mouse model at an exposure near the intended human therapeutic exposure.
IB/0019	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/12/2015	n/a		

PSUSA/10180 /201503	Periodic Safety Update EU Single assessment - cabozantinib	06/11/2015	n/a		PRAC Recommendation - maintenance
II/0015	Update of sections 4.8 and 5.1 of the SmPC following the results of study XL184-301. The Risk Management Plan version 3 and the Package Leaflet and RMP are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	11/01/2016	SmPC and PL	
II/0011/G	This was an application for a group of variations. Update of sections 4.2 and 5.2 of the SmPC further to the results of studies conducted to assess the pharmacokinetics of cabozantinib in subjects with impaired hepatic and renal function. The PL is proposed to be updated accordingly. The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet. 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	23/04/2015	27/05/2015	SmPC and PL	In this group of variations the MAH updated information on dosing in patients with hepatic and renal impairment indicating that in cases of mild or moderate hepatic impairment the recommended dose of cabozantinib needs to be lower than recommended 140 mg (60 mg once daily), while in patients with mild or moderate renal impairment cabozantinib should be used with caution. The medicine is not recommended for use in patients with severe hepatic and renal impairment.
II/0013/G	This was an application for a group of variations.	23/04/2015	27/05/2015	SmPC	In this variation the MAH provided results from two non-

	Submission of non-clinical study reports from Enterohepatic recirculation evaluation in dogs (XL184-NC-045) and Enterohepatic recirculation evaluation in rats (XL184-NC-046). The requested group of variations proposed no amendments to the Product Information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				clinical studies evaluating the enterohepatic recirculation, excretion and metabolite profiles of cabozantinib. Based on the results the SmPC has been updated to reflect possibility of drug-drug interactions of cabozantinib and bile salt-sequestering agents such as cholestyramine and cholestagel. Such agents may impact absorption (or reabsorption) resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown.
IB/0014	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	14/04/2015	n/a		
PSUSA/10180 /201409	Periodic Safety Update EU Single assessment - cabozantinib	10/04/2015	n/a		PRAC Recommendation - maintenance
II/0012	Submission of the final study report from a non-clinical toxicity study of cabozantinib in younger juveniles (XL184-NC-040) C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
R/0009	Renewal of the marketing authorisation.	20/11/2014	19/01/2015	SmPC and	The CHMP, having reviewed the available information on

				Annex II	the status of the fulfilment of Specific Obligation and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Cometriq, subject to the Specific Obligation and Conditions as laid down in Annex II to the Opinion.
II/0007/G	This was an application for a group of variations. Submission of nonclinical study reports conducted further to CHMP recommendation to perform in vitro experiments to further characterise metabolite M2a (EXEL-1644; 6-desmethyl amide cleavage product sulfate): nonclinical pharmacology study evaluating the on-target kinase inhibition potential of cabozantinib metabolites (Study EXL087); in vitro studies investigating CYP inhibition and drug transporter interactions involving cabozantinib metabolite EXEL-1644 (Studies EXEL1644-NC-006, EXEL1644-NC-007, EXEL1644-NC-008, EXEL1644-NC-010, EXEL1644-NC-011); in vitro metabolism study investigating sulfotransferases involved in the formation of metabolites EXEL-1644 and EXEL-1646 (Study EXEL1644-NC-009). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	18/12/2014	n/a		

	of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0005/G	This was an application for a group of variations. Update of sections 4.4 and 4.5 of the SmPC with regards to concomitant use with MRP2 inhibitors further to the results of Study XL184-NC-039 evaluating Cabozantinib as a Substrate and Inhibitor of a Panel of Human Drug Transporters (MEA 006). The Package leaflet is updated accordingly; Submission of the results of Study XL184-NC-043 assessing cabozantinib as an inhibitor of human MATE1 and MATE2-K-mediated transport (MEA 007); Submission of the results of Study XL184-NC-048 assessing cabozantinib as an inhibitor of human OAT3, MATE1, and MATE2-K-mediated transport.	18/12/2014	27/05/2015	SmPC and PL	

	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 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0006	Update of section 4.4 of the SmPC to delete the warning on concomitant use with proton pump inhibitors further to the results of a drug-drug Interaction Study XL184-018 with medicinal products affecting gastric pH (esomeprazole and Famotidine) (MEA 004). The Package leaflet is updated accordingly. The MAH also took the opportunity to make a correction in section 4.5 and the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	19/01/2015	SmPC and PL	
II/0004/G	This was an application for a group of variations. 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	25/09/2014	19/01/2015	SmPC	

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0003	To extend the shelf-life of the finished product 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)	17/06/2014	19/01/2015	SmPC	To extend the shelf-life of the finished product
IB/0002	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	28/05/2014	19/01/2015	SmPC, Labelling and PL	
IA/0001	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	28/04/2014	19/01/2015	SmPC	