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
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

[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).

					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	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

	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				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	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

	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				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. 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	23/04/2015	27/05/2015	SmPC	In this variation the MAH provided results from two non-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	14/04/2015	n/a		

	material/intermediate/reagent - Other variation				
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 Annex II	The CHMP, having reviewed the available information on 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	18/12/2014	n/a		

	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 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.	18/12/2014	27/05/2015	SmPC and PL	

	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. 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.	25/09/2014	19/01/2015	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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 data 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	
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	