XALKORI

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
IB/0061	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	28/02/2019		SmPC and PL	
II/0055	Update of section 4.2 of the SmPC in order to provide greater clarity in the crizotinib dose adjustments for patients who receive a reduced dose of crizotinib, either because of pre-existing moderate or severe	20/09/2018	23/10/2018	SmPC and PL	If dose reduction is necessary for patients treated with crizotinib 250 mg orally twice daily, the dose should be reduced as follows: • First dose reduction: XALKORI 200 mg taken orally

[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).

	hepatic impairment or severe renal impairment or because of a previous dose reduction while on treatment with crizotinib. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				twice daily • Second dose reduction: XALKORI 250 mg taken orally once daily • Permanently discontinue if patient is unable to tolerate XALKORI 250 mg taken orally once daily Clarifications were also made on dosing regimen modification recommendations for patients who experience hematologic or non-hematologic toxicities while on treatment with crizotinib. The recommendation for dosing regimen modification stating “resume at 200 mg twice daily” is revised to “resume at the next lower dose” where the next dose level is already provided in the text above.
IB/0060/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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) B.II.f.1.e - Stability of FP - Change to an approved stability protocol	18/09/2018	23/10/2018	SmPC	
II/0057	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/09/2018	n/a		
II/0058	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/09/2018	n/a		
T/0059	Transfer of Marketing Authorisation	30/07/2018	31/08/2018	SmPC,	

				Labelling and PL	
IG/0938/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.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)	13/07/2018	n/a		
II/0054	Update of section 5.1 of the SmPC to reflect the final analysis of overall survival (OS), a secondary endpoint, in Study A8081014, a randomized phase 3 trial comparing oral crizotinib to first line chemotherapy in patients with ALK-positive advanced	21/06/2018	31/08/2018	SmPC	Section 5.1 of the SmPC has been updated to reflect the final analysis of overall survival (OS), a secondary endpoint in Study A8081014. The analysis shows that there was a numerical improvement in overall survival in the patients treated with crizotinib, although this improvement was not

	non-squamous non-small cell lung cancer (NSCLC). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				statistically significant.
II/0053/G	This was an application for a group of variations. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	08/03/2018	n/a		
PSUSA/10042 /201708	Periodic Safety Update EU Single assessment - crizotinib	08/03/2018	n/a		PRAC Recommendation - maintenance
II/0051	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	31/08/2018	SmPC and Labelling	Coadministration of crizotinib with strong CYP3A inhibitors is expected to increase crizotinib plasma concentrations. Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib area-under-the-plasma-concentration versus time curve from time zero to infinity (AUCinf) and maximum observed plasma concentration (Cmax) values that were approximately 3.2 fold and 1.4 fold, respectively, those seen when crizotinib was administered alone. Coadministration of repeated doses of crizotinib (250 mg

					once daily) with repeated doses of itraconazole (200 mg once daily), a strong CYP3A inhibitor, resulted in increases in crizotinib steady-state AUCtau and Cmax, that were approximately 1.6-fold and 1.3-fold, respectively, those seen when crizotinib was administered alone. Therefore, the concomitant use of strong CYP3A inhibitors (including but not limited to atazanavir, ritonavir, cobicistat, itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, and erythromycin) should be avoided. Unless the potential benefit to the patient outweighs the risk, in which case patients should be closely monitored for crizotinib adverse events (see section 4.4). Physiologically-based pharmacokinetic (PBPK) simulations predicted a 17% increase in crizotinib steady-state AUC after treatment with the moderate CYP3A inhibitors, diltiazem or verapamil. Caution is therefore recommended in case of coadministration of crizotinib with moderate CYP3A inhibitors. Finally in line with the current recommendations in sections 4.2 and 4.5 of the SmPC, a new warning has been included in section 4.4 of the SmPC that grapefruit or grapefruit juice should be avoided as it may increase plasma concentrations of crizotinib
II/0050	Update of sections 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC in order to update the information about hepatic impairment based on the results of study A8081012 which evaluated the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib in advanced cancer patients. The package leaflet is updated accordingly. In addition, RMP version 7.4 is being updated.	14/12/2017	18/01/2018	SmPC and PL	Based on the result of study A8081012, treatment with crizotinib should be used with caution in patients with hepatic impairment. Based on the National Cancer Institute (NCI) classification, no starting dose adjustment of crizotinib is recommended for patients with mild hepatic impairment (either AST > Upper Limit of Normal (ULN) and total bilirubin ≤ULN or any AST and total bilirubin >ULN but The starting crizotinib dose for patients with moderate

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				hepatic impairment (any AST and total bilirubin >1.5 × ULN and ☐ The starting crizotinib dose for patients with severe hepatic impairment (any AST and total bilirubin >3 × ULN) is recommended to be 250 mg once daily. Crizotinib dose adjustment according to Child-Pugh classification has not been studied in patients with hepatic impairment. Section 4.2, 4.3, 4.4, 4.8 and 5.2 were updated to reflect these recommendations, the results from study A8081012 and remove the contraindication of crizotinib in severe hepatic impairment.
II/0049/G	This was an application for a group of variations. Update of Annex II of the marketing authorisation to remove Therapeutic Management Guide from the Xalkori educational materials based on the submission of the final results of the Non-Interventional Post-Authorisation Safety Study (PASS) A8081049 “A cross-sectional study to evaluate the effectiveness of Xalkori Therapeutic Management Guide among physicians prescribing Xalkori in Europe”. The final results of PASS A8081050 “A cross-sectional study to evaluate the effectiveness of Xalkori Patient Information Brochure among non-small cell lung cancer (NSCLC) patients receiving Xalkori treatment in Europe” was also submitted. The MAH also took the opportunity to state “monotherapy” in section 4.1 of the SmPC to bring the SmPC in line with the latest QRD template as requested by CHMP. Annex IIIA is also updated to add information related to the unique identifier.	06/07/2017	18/01/2018	SmPC, Annex II and Labelling	The MAH submitted the final results from PASS studies A8081049 and A8081050 that have the aim respectively to evaluate the effectiveness of the Educational Material with doctors (Therapeutic Management Guide) and patients (Patient Information Brochure). Results of Study A8081049 showed that the majority of doctors were aware of the associated risks with Xalkori. Since the information contained in the Xalkori Therapeutic Management Guide is also included in the SmPC, the MAH’s proposal to remove the Therapeutic Management Guide from the educational material was endorsed. Annex II of the marketing authorisation was therefore updated accordingly. Results of Study A8081050 indicated the Patient Information Brochure is an effective channel for communicating information to patients on risks associated with XALKORI and the Committee agreed it should be maintained.

	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				
PSUSA/10042 /201608	Periodic Safety Update EU Single assessment - crizotinib	09/03/2017	n/a		PRAC Recommendation - maintenance
II/0044	Update of section 5.1 of the SmPC in order to provide the results of the final Progression Free Survival (PFS), Objective Response Rate (ORR), Duration of Response (DR) and Overall Survival (OS) analysis in Study A8081007 (SOB001). The data submitted fulfils the specific obligation SOB 001 and the Conditional Marketing Authorisation is switched to a Marketing Authorisation not subject to specific obligations. The Risk Management Plan (v.7.2) is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	11/11/2016	SmPC	
IA/0047	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	27/10/2016	n/a		
IB/0046	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	18/10/2016	n/a		

	authorisation, including the RMP - Other variation				
II/0039	Extension of Indication to include treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC) based on the results of Study A8081001 (a multinational, multicenter, open-label, single-arm study of the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of crizotinib in patients with advanced cancer). Consequential changes are proposed to SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 and the Package Leaflet is proposed to be updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Annex II. An updated RMP version 7.1 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/07/2016	25/08/2016	SmPC, Annex II and PL	Please refer to the scientific discussion 'Xalkori EMEA/H/C/02489/II/0039'.
II/0034	Update of section 4.4 and 4.8 of the SmPC with information on the effect of crizotinib on renal function, based on the data reviewed in studies A8081001, A8081005, A8081007 and A8081014. The Package Leaflet has been updated accordingly. Furthermore, minor editorial changes have been introduced in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2016	01/08/2016	SmPC and PL	

R/0041	Renewal of the marketing authorisation.	26/05/2016	29/07/2016	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 XALKORI, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IA/0045	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	11/07/2016	n/a		
IA/0043/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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	31/05/2016	n/a		
II/0038	Update of sections 4.4 and 4.5 of the SmPC based on	26/05/2016	29/07/2016	SmPC and PL	The concomitant use of crizotinib with strong CYP3A4

	the rifampicin DDI substudy report, a study undertaken in order to evaluate the effect of rifampicin (a strong inducer of CYP3A) on multiple-dose PK of crizotinib in advanced cancer patients. The provision of the study report addresses a part of the post-authorisation measure MEA 009. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Czech Republic, Norway and Sweden in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				inhibitors or with strong and moderate CYP3A4 inducers should be avoided. Coadministration of repeated doses of crizotinib (250 mg twice daily) with repeated doses of rifampicin (600 mg once daily), a strong CYP3A4 inducer, resulted in 84% and 79% decreases in crizotinib steady state AUCtau and Cmax, respectively, compared to when crizotinib was given alone. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's wort, should be avoided. The effect of a moderate inducer including but not limited to efavirenz or rifabutin is not clearly established therefore, their combination with crizotinib should be also avoided.
PSUSA/10042 /201508	Periodic Safety Update EU Single assessment - crizotinib	01/04/2016	26/05/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10042/201508.
II/0040	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/05/2016	n/a		
IA/0042/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	04/04/2016	n/a		

	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.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.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)				
II/0024	For further information please refer to the published Assessment Report: Xalkori H-2489-II-24-AR. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/10/2015	23/11/2015	SmPC, Annex II and PL	Extension of Indication to add first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) based on the results of the pivotal Study A8081014; a multinational, multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of crizotinib to first-line chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in patients with previously untreated ALK-positive advanced non-squamous NSCLC, as well as updated safety results from Studies A8081001, A8081005 and A8081007. As a result sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial and QRD-template related changes in the SmPC, Annex II and Package Leaflet. A revised RMP version 6.2 was agreed during the procedure.

II/0033	Update the SmPC section 5.1 with revised efficacy data based on results from study A8081007. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	26/05/2016	SmPC	In this variation the MAH corrected the values of the composite endpoint of time to deterioration in patients treated with Xalkori who reported symptoms of pain in chest, dyspnoea, or cough. The reanalysis followed the identification of issues originating from the implementation of censoring rules according to the statistical analysis plan and handling of missing assessments. Revised values did not affect the interpretation of the study results.
PSUSA/10042 /201502	Periodic Safety Update EU Single assessment - crizotinib	24/09/2015	19/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10042/201502.
IB/0036	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2015	26/05/2016	Annex II	
II/0032	Submission of the report on response to crizotinib in patients with anaplastic lymphoma kinase (ALK)-negative non-small cell lung cancer (NSCLC) from study A8081001 in order to fulfil a post-approval recommendation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/09/2015	n/a		
IB/0035	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	10/09/2015	n/a		

R/0026	Renewal of the marketing authorisation.	21/05/2015	17/07/2015		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 Xalkori, subject to the Specific Obligation and Conditions as laid down in Annex II to the Opinion.
IAIN/0031/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.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	23/06/2015	n/a		
IB/0030/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the	12/06/2015	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0021	Update of section 4.8 of the SmPC to include the results of an ophthalmological substudy (A8081001-ophtalmological report) with crizotinib. 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	17/07/2015	SmPC	
IA/0028	A.7 - Administrative change - Deletion of manufacturing sites	15/04/2015	n/a		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/04/2015	17/07/2015	PL	
PSUSA/10042 /201408	Periodic Safety Update EU Single assessment - crizotinib	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0025/G	This was an application for a group of variations. Submission of a revised RMP version 5.3 in order to: - change the CYP3A inhibitor from ketoconazole to itraconazole in Study A8081001; - and to change the due date for completion of MEA 009 (“The MAH should submit DDI studies with ketoconazole or rifampin at steady-state in order to allow defining dosing adjustments in case of coadministration.”). C.I.11.z - Introduction of, or change(s) to, the	26/02/2015	n/a		The variation lead to no changes to the product information.

	obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0022	Update of sections 4.8 and 5.2 of the SmPC to reflect results of an ECG substudy report from Study A8081007 and Study A8081005. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/01/2015	17/07/2015	SmPC	This application for a type II variation proposed revision to the XALKORI SmPC, Section 4.8 Undesirable effects (QT interval prolongation) and Section 5.2 Pharmacokinetic properties (Cardiac electrophysiology), to add new QTc and heart rate (HR) data from results of an ECG substudy. The following information on the ECG sub-study was included in the SmPC: An ECG substudy using blinded manual ECG measurements was conducted in 52 ALK-positive NSCLC patients who received crizotinib 250 mg twice daily. Eleven (21%) patients had an increase from Baseline in QTcF value ≥ 30 to < 60 msec and 1 (2%) patient had an increase from Baseline in QTcF value of ≥ 60 msec. No patients had a maximum QTcF ≥ 480 msec. The central tendency analysis indicated that all upper limits of the 90% CI for the LS mean change from Baseline in QTcF at all Cycle 2 Day 1 time points were < 20 msec. A pharmacokinetic/pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc. In addition, a decrease in heart rate was found to be associated with increasing crizotinib plasma concentration (see section 4.4), with a maximum mean reduction of 17.8 beats per minute (bpm) after 8 hours on Cycle 2 Day 1.
PSUV/0017	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance

R/0015	Renewal of the marketing authorisation.	26/06/2014	22/08/2014	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 Xalkori, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IB/0020/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/08/2014	n/a		
II/0016	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	17/07/2015	SmPC and PL	
IA/0018/G	This was an application for a group of variations. 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	14/07/2014	n/a		

	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 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.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				
PSUV/0012	Periodic Safety Update	20/03/2014	14/05/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0012.
IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/04/2014	n/a		
II/0004	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to reflect updated efficacy and safety data from studies A8081001 and A8081005 and data from the comparative phase III study A8081007 in order to fulfil the obligation to conduct post – authorisation measures and to partially address the conditions imposed to the marketing authorisation. The Annex II and Package Leaflet are updated accordingly. C.I.4 - Variations related to significant modifications of	20/02/2014	21/03/2014	SmPC, Annex II and PL	The MAH submitted the CSR for study A8081007, a randomized, open-label, comparative study of the efficacy and safety of crizotinib versus standard of care chemotherapy in ALK-positive patients with NSCLC. A large and clinically relevant effect on PFS is observed (7.7 months [95% CI: 6.0, 8.8] vs 3.0 months [95% CI: 2.6, 4.3]) in this study however OS data is still immature. In addition, the MAH submitted updated safety (SAEs and deaths) and efficacy (PFS and OS) data from 2 multicentre, multinational, single-arm studies (A8081001 and A8081005). The updated data confirms the efficacy and safety profile established at

	the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				the time of initial marketing authorisation. Based on the data submitted, it is confirmed that hepatotoxicity is an important identified risk and that liver function tests should be performed once a week during the first 2 months of treatment.
II/0013	Update of section 5.3 of the SmPC in order to correct safety margins for systemic toxicities. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	21/03/2014	SmPC	Safety margin values for systemic toxicities were corrected by adjusting the human systemic exposure value used in the exposure margin calculation. Consequently, the values in section 5.3 of the SmPC have been corrected. This adjustment in Safety Margins is not considered to have an impact on the nonclinical safety profile of Crizotinib.
II/0009/G	This was an application for a group of variations. Group of variations related to the introduction of a new manufacturing site for the active substance (crizotinib) including the following changes: A.4. – change of the name of a supplier of the raw material used in the synthesis of the active substance B.I.a.1.c – addition of an alternative manufacturer and release site of crizotinib with consequential changes related to the manufacturing process at this site B.I.b.1.z – change of the specification limit from a raw material used in the synthesis of crizotinib 7 x B.I.b.2.e – introduction of alternative tests methods or replacement of in-process test methods used to control the quality of the active substance, reagents and starting materials A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	20/02/2014	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions 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.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a				

	test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0007	Update of sections 4.2, 4.4 and 5.2 to propose an adjustment of the dose of crizotinib in patients with severe renal impairment further to the results of study A8081020. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/12/2013	29/01/2014	SmPC and PL	In study A8081020 evaluating the effect of severe renal impairment on the single dose PK of crizotinib, values for crizotinib AUCinf and Cmax based on geometric means in subjects with severe renal impairment increased by 79% and 34%, respectively, compared to those with normal renal function. It is therefore recommended to adjust the crizotinib dose to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or haemodialysis. The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment. Sections 4.2, 4.4 and 5.2 of the SmPC are updated.
IB/0011	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	22/11/2013	n/a		
II/0005/G	This was an application for a group of variations. Update of sections 4.2 and 5.2 of the SmPC to reflect the results of population modelling analysis plan of the main studies 1001, 1005 and 1007 on special patient groups. Update of sections 4.5 and 5.2 to reflect the outcome	24/10/2013	29/01/2014	SmPC and PL	The Population pharmacokinetic analysis in patients with non-small cell lung cancer conducted by the MAH confirmed there is no need to adjust the dose in patients with mild or moderate renal impairment. The very limited data in patients with severe renal impairment and end-stage renal disease did not allow determining the need for dose adjustment. This analysis showed that age, body weight and gender have no

	of in vitro studies investigating the effect of crizotinib on UGT and as inhibitor of BSEP and renal uptake transporters. Update of sections 4.5 and 5.2 to reflect the outcome of a drug-drug interaction study with proton-pump inhibitors and H2 antagonists. The Package leaflet is updated accordingly. In addition, the MAH took the opportunity of this group of variations to include minor editorial changes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				clinically meaningful effect on crizotinib pharmacokinetics. An in vitro study evaluating the effect of crizotinib as an inhibitor of BSEP and renal secretory transporters confirmed that crizotinib is an inhibitor of OCT1 and OCT2 and could increase plasma concentrations of co-administered drugs that are substrates of these transporters. However crizotinib did not inhibit OAT1 or OAT3. The in vitro study investigating the effect of crizotinib on UGT (notably UGT1A1) indicated that crizotinib is a weak inhibitor of UGT1A1 and UGT2B7 and may potentially increase plasma concentrations of co-administered drugs metabolised predominantly by UGT1A1 or UGT2B7. Drug-drug interaction studies with proton pump inhibitor (PPI) and H2 antagonists were conducted. The extent of the change in total exposure of crizotinib observed in these studies was not clinically meaningful and therefore co-administration of PPI and H2 antagonists does not require dose adjustment.
R/0006	Renewal of the marketing authorisation.	27/06/2013	26/08/2013		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 XALKORI, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
N/0008	Minor change in labelling or package leaflet not	19/07/2013	29/01/2014	PL	

	connected with the SPC (Art. 61.3 Notification)				
II/0002	Update of sections 4.5 and 5.2 of the SmPC in order to include the outcome of in vitro studies indicating that crizotinib is an inhibitor of CYP2B6 and may be an inducer of CYP3A4. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. The MAH took also the opportunity of this variation to introduce editorial changes in the SmPC and to correct discrepancies between section 4 of the PL and section 4.8 of the SmPC regarding frequency of rash, and leukopenia. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	26/08/2013	SmPC, Annex II and PL	Study XT123005 investigating the potential for crizotinib to induce CYP3A4 and CYP2B6 in vitro using cryopreserved human hepatocytes was not conclusive and did not rule out the potential role of crizotinib as an inducer of CYP3A4. Study XT125002 investigated the potential for crizotinib to inhibit CYP2B6 activity in vitro, using pooled human liver microsomes. Sections 4.5 and 5.2 of the SmPC were updated to reflect the role of crizotinib as an inhibitor of CYP2B6 and as a potential inducer of CYP3A4. The PL was updated accordingly.
IB/0003	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	28/01/2013	26/08/2013	SmPC	
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
