TAGRISSO

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/0054	Update of section 4.8 of the SmPC to add 'Skin Hyperpigmentation' to the list of adverse drug reactions (ADRs) with frequency 'uncommon' based on literature. The Package leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives	08/02/2024		SmPC and PL	Section 4.8 is updated to add "Skin hyperpigmentation" (overall frequency (all CTCAE grades): uncommon (0.8%), frequency of CTCAE grade 3 or higher: 0) with a footnote reflecting that "Cases of erythema dyschromicum perstans have been reported in the post-marketing setting".

[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				
II/0052	Update of section 5.1 of the SmPC in order to update efficacy information (final OS data) based on final results from study D5164C00001 (ADAURA) listed as a PAES in the Annex II; this is a Phase III, double-blind, randomised, placebo-controlled study, designed to assess the efficacy and safety of osimertinib versus placebo in the adjuvant setting in patients with stage IB-IIIA epidermal growth factor receptor mutation positive (EGFRm) non-small cell lung cancer (NSCLC) who have undergone complete tumour resection, with or without postoperative adjuvant chemotherapy. Annex II has also been updated accordingly to remove this study. The RMP version 15.2 is approved. In addition, the MAH took the opportunity to implement editorial changes to the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/09/2023		SmPC and Annex II	SmPC new text The final analysis of OS for the adjuvant treatment of EGFR mutation-positive NSCLC, with or without prior adjuvant chemotherapy, demonstrated a statistically significant improvement in OS for patients treated with TAGRISSO compared to placebo for both the stage II-IIIA population (100 OS events [21% maturity]; HR=0.49; 95.03% CI: 0.33, 0.73; p-value=0.0004) and the overall population (IB-IIIA; 124 OS events [18% maturity]; HR=0.49; 95.03% CI: 0.34, 0.70; p-value < 0.0001). For both populations, the median OS was not reached in either treatment arm and the 95% CIs were not calculable. The median follow-up time for OS in all patients was 59.9 months (stage II-IIIA population) and 60.4 months (stage IB-IIIA population) in the TAGRISSO arm and 56.2 months (stage II-IIIA population) and 59.4 months (stage IB IIIA population) in the placebo arm. For more information, please refer to the Summary of Product Characteristics.
II/0050	Update of sections 4.2, 4.4 and 4.8 of the SmPC to add toxic epidermal necrolysis (TEN) as a new adverse drug reactions (ADRs) with frequency uncommon and to include corresponding warning	22/06/2023	26/07/2023	SmPC, Annex II and PL	SmPC new text Update of section 4.8 to include Toxic epidermal necrolysis (TEN) as a new adverse reaction, with the frequency unknown. As a result, sections 4.2 and 4.4 are also

	and related dose modification in the posology section, and to update the frequency of interstitial lung disease (ILD) based on an internal safety information review. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				updated to reflect that Tagrisso should be interrupted if signs and symptoms of TEN appear and should be discontinued if TEN is diagnosed. Furthermore, the frequency of interstitial lung disease has been updated in section 4.8 based on the addition of Organising Pneumonia to the interstitial lung disease umbrella term. For more information, please refer to the Summary of Product Characteristics.
IB/0051/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 of the AS 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.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.z - Change in the specification parameters and/or limits of an AS, starting	07/06/2023	n/a		

	material/intermediate/reagent - Other variation B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.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 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				
II/0047	Update of section 5.2 of the SmPC based on final results from studies ODIN-BM and ODIN-HV; these are two phase I clinical pharmacology studies conducted in EGFRm+ NSCLC patients (ODIN-BM) and healthy volunteers (ODIN-HV) to determine osimertinib blood-brain barrier (BBB) penetration and brain distribution in patients with brain metastases and healthy volunteers with an intact BBB, respectively. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/10/2022	26/07/2023	SmPC	SmPC new text
IB/0049/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 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.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	23/09/2022	n/a		

	variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
PSUSA/10472 /202111	Periodic Safety Update EU Single assessment - osimertinib	21/07/2022	19/09/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10472/202111.
IA/0048	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/07/2022	n/a		
R/0044	Renewal of the marketing authorisation.	27/01/2022	24/03/2022	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of TAGRISSO in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0045	Update of section 5.3 of the SmPC in order to reflect the outcome of the 104 Week Oral (Gavage) Carcinogenicity Study (507363) in the Rat submitted as recommended by the CHMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	27/01/2022	24/03/2022	SmPC	An increased incidence of proliferative vascular lesions (angiomatous hyperplasia and haemangioma) in the mesenteric lymph node was observed in the rat 104-week carcinogenicity study at exposures 0.2 times the AUC at the recommended clinical dose of 80 mg once daily, and is unlikely to be relevant for humans. For more information, please refer to the Summary of

	data				Product Characteristics.
IB/0043/G	This was an application for a group of variations. 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.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/06/2021	n/a		
II/0039/G	This was an application for a group of variations. Extension of indication of Tagrisso to include the adjuvant treatment after complete tumour resection in EGFR mutant non-small cell lung cancer (NSCLC) patients, based on the results from the pivotal Phase 3 randomised, placebo-controlled study ADAURA (D5164C00001); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 14.3 of the RMP has also been agreed. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a	22/04/2021	21/05/2021	SmPC and PL	Please refer to Scientific Discussion 'Tagrisso-H-C-004124-II-0039'

	specification parameter which may have a significant effect on the overall quality of the AS and/or the FP C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0042	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	24/02/2021	n/a		
IB/0041	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	08/01/2021	n/a		
IAIN/0040/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	18/09/2020	n/a		
II/0037	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/09/2020	09/03/2021	SmPC	
IB/0038/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	17/07/2020	n/a		

	variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size				
II/0036	Update of section 5.1 of the SmPC in order to update	25/06/2020	09/03/2021	SmPC, Annex	The results of the final OS analysis in AURA3 (DCO4 of 15

	the information regarding overall survival (OS) based on the final results from study D5160C00003 (AURA3); this is a randomized study of osimertinib versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer whose disease has progressed with previous EGFR TKI. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			II and Labelling	March 2019; 67.1% maturity for OS overall) have been reflected in section 5.1 of the SmPC. Osimertinib demonstrated a numerical advantage in OS compared to chemotherapy, which did not reach statistical significance (HR=0.87 [95.564% CI: 0.67, 1.13]; p=0.277). The median OS was 26.8 months (95% CI: 23.49, 31.54) in the osimertinib arm and 22.5 months (95% CI: 20.17, 28.81) in the chemotherapy arm. The interpretation of the OS results from this study is confounded by the fact that a large proportion of patients in the chemotherapy arm crossed over to receive treatment with osimertinib after RECIST progression (99/140 [70.7%]). For more information, please refer to the Summary of Product Characteristics.
PSUSA/10472 /201911	Periodic Safety Update EU Single assessment - osimertinib	11/06/2020	n/a		PRAC Recommendation - maintenance
IB/0035	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	08/05/2020	n/a		
II/0032	Update of section 4.8 of the SmPC in order to include erythema multiforme as an adverse drug reaction following the review of the MAH internal safety data. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity of this procedure to add the event frequency of Stevens-Johnson syndrome to align with the approved text in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to	02/04/2020	09/03/2021	SmPC and PL	Four (4) cases of erythema multiforme have been reported in clinical trials and 30 cases post marketing, 10 of which with mucosal involvement. Based on an analysis of disproportionality between treatment arms in the clinical trial data and one case of positive rechallenge post marketing, the SmPC section 4.8 has been updated in order to reflect erythema multiforme as an adverse drug reaction with an uncommon frequency. The PL has been updated accordingly.

	new quality, preclinical, clinical or pharmacovigilance data				
II/0033	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/03/2020	09/03/2021	SmPC and Labelling	
II/0029	Update of sections 4.2 and 5.2 of the SmPC in order to reflect the outcome of study D5160C00035, an open-label, Phase I study to assess the pharmacokinetics, safety and tolerability of osimertinib following a single oral 80 mg dose to patients with advanced solid tumours and normal renal function or severe renal impairment. This study was a Category 3 study in the EU-RMP. The RMP version 13 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/09/2019	24/10/2019	SmPC	In a clinical trial, patients with severe renal impairment (CLcr 15 to less than 30 mL/min; n=7) compared to patients with normal renal function (CLcr greater than or equal to 90 mL/min; n=8) after a single 80 mg oral dose of TAGRISSO showed a 1.85-fold in AUC (90% CI; 0.94, 3.64) and a 1.19-fold increase in Cmax (90% CI: 0.69, 2.07). However based on data from clinical trials and population PK analysis, no dose adjustments are necessary in patients with severe renal impairment.
II/0031	Update of section 4.8 of the SmPC to include onychalgia in the list of associated clustered terms for paronychia further to a MAH internal safety information review. 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	19/09/2019	24/10/2019	SmPC and PL	

PSUSA/10472 /201811	Periodic Safety Update EU Single assessment - osimertinib	27/06/2019	26/08/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10472/201811.
IA/0030	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	28/06/2019	n/a		
II/0026	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	31/01/2019	n/a		
IB/0027/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 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/12/2018	n/a		

II/0024	Update of sections 4.2 and 5.2 of the SmPC based on the results from Study D5160C00008, undertaken to determine the pharmacokinetics, safety and tolerability of AZD9291 following a single oral dose to patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment. An updated RMP version 11 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/07/2018	31/08/2018	SmPC	In the clinical trial, patients with different types of advanced solid tumours and with mild hepatic impairment (Child Pugh A, mean score = 5.3, n=7) or moderate hepatic impairment (Child Pugh B, mean score = 8.2, n=5) had no increase in exposure compared to patients with normal hepatic function (n=10) after a single 80 mg dose of Tagrisso. The geometric mean ratio (90% CI) of osimertinib AUC and Cmax was 63.3% (47.3, 84.5) and 51.4% (36.6, 72.3) in patients with mild hepatic impairment and 68.4% (49.6, 94.2) and 60.7% (41.6, 88.6) in patients with moderate hepatic impairment; for the metabolite AZ5104 the AUC and Cmax were 66.5% (43.4, 101.9) and 66.3% (45.3, 96.9) in patients with mild hepatic impairment and 50.9% (31.7, 81.6) and 44.0% (28.9, 67.1) in patients with moderate hepatic impairment, compared to the exposure in patients with normal hepatic function. Based on these data, the CHMP concluded that no dose adjustments are necessary in patients with mild hepatic impairment (Child Pugh A) or moderate hepatic impairment (Child Pugh B). Similarly, based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤upper limit of normal (ULN) and aspartate aminotransferase (AST) >ULN or total bilirubin >1.0 to 1.5x ULN and any AST) or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST).
II/0023	Submission of an updated RMP version 9 in order to remove the category 3 PASS Study D5160C00022 (ASTRIS) from the Pharmacovigilance plan.	12/07/2018	n/a		

	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				
II/0022	Submission of an updated RMP version 9 in order to remove the category 3 PASS D5165C00001 (CAURAL) from the Pharmacovigilance Plan due to its early termination. 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	14/06/2018	n/a		n/a
II/0021	Update of SmPC sections 4.5 and 5.2 to reflect the results of Study D5160C00036, undertaken to assess the effect of single and multiple oral doses of osimertinib on the pharmacokinetics of a P-glycoprotein probe drug (Fexofenadine) in patients with advanced EGFRm NSCLC that have progressed on a prior EGFR-TKI regimen. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make a correction in Annex II and to implement minor editorial and/or QRD-template related changes in the SmPC and Package Leaflet. A revised RMP version 9 was provided as	14/06/2018	31/08/2018	SmPC, Annex II and PL	In a clinical Pregnane X Receptor (PXR) interaction study, co-administration of TAGRISSO with fexofenadine (P-gp substrate) increased the AUC and Cmax of fexofenadine by 56% (90% CI 35, 79) and 76% (90% CI 49, 108) after a single dose and 27% (90% CI 11, 46) and 25% (90% CI 6, 48) at steady state, respectively. Patients taking concomitant medications with disposition dependent upon P-gp and with narrow therapeutic index (e.g. digoxin, dabigatran, aliskiren) should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO.

	part of the application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10472 /201711	Periodic Safety Update EU Single assessment - osimertinib	14/06/2018	n/a		PRAC Recommendation - maintenance
II/0019	Extension of Indication to include (as monotherapy) first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, based on data from the FLAURA study (D5160C00007); a phase III, double-blind, randomised study to assess the efficacy and safety of AZD9291 versus a standard of care epidermal growth factor receptor-Tyrosine Kinase Inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic non-small-cell lung cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, sections 4.4 and 4.8 of the SmPC have been updated with a new warning with regard to increased risk of developing adverse events of Grade 3 or higher in patients > 65 years and <50 kg. In addition, the MAH took the opportunity to update sections 2 and 4.4 of the SmPC with information regarding the excipient sodium, and to implement editorial changes	26/04/2018	07/06/2018	SmPC and PL	For further information please refer to the published Assessment Report: Tagrisso H-4124-II-19-AR

	in the SmPC and Package Leaflet. An updated RMP version 10.0 was agreed during the procedure. Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0025	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	04/05/2018	n/a		
PSUSA/10472 /201705	Periodic Safety Update EU Single assessment - osimertinib	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0018	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	14/11/2017	n/a		
II/0016	Provision of the final CSR for Study Aura 17; a phase II, open label, single-arm study to assess the safety and efficacy of AZD9291 in Asia pacific patients with locally advanced/metastatic non-small cell lung cancer whose disease has progressed with previous	06/07/2017	n/a		N/A

	epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours harbour a T790M mutation within the epidermal growth factor receptor gene). An updated RMP version 7.0 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0015	Update of section 5.2 of the SmPC to include data from studies performed to investigate human plasma protein binding (Study No. BS001265-53-AZD9291), the assessment of non-specific incubational binding in transporter inhibition assays (Study No. BS000760-92) and the implications on transporter DDI risk assessment. In addition, the MAH took the opportunity to implement minor updates and editorial changes in the SmPC and to update the address of the MAH and manufacturer in SmPC section 7, the labelling and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/07/2017	07/06/2018	SmPC, Labelling and PL	In vitro, plasma protein binding of osimertinib is 94.7% (5.3% free). In vitro, osimertinib does not inhibit OAT1, OAT3, OATP1B1, OATP1B3, MATE1, OCT2 and MATE2K at clinically relevant concentrations.
II/0014/G	This was an application for a group of variations. Update of section 5.3 of the SmPC to include information regarding CNS distribution based on non-clinical data.	06/07/2017	07/06/2018	SmPC	Osimertinib penetrated the intact blood-brain barrier of the cynomolgus monkey (i.v. dosing), rat and mouse (oral administration).

	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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10472 /201611	Periodic Safety Update EU Single assessment - osimertinib	09/06/2017	n/a		PRAC Recommendation - maintenance
II/0009/G	This was an application for a group of variations. Update of SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2 based on the results from study D5160C00003 (AURA3) and the updated CSRs for studies D5160C00001 (AURAex) and D5160C00002 (AURA2). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet. The provision of the CSR from study AURA3 addressed the remaining Specific Obligation for Tagrisso and hence it is recommended to convert the Marketing Authorisation from a Conditional Marketing Authorisation to a Marketing	23/02/2017	24/04/2017	SmPC and PL	Please refer to Scientific Discussion Tagrisso-H-C-4124-II-09-G

	Authorisation not subject to Specific Obligations. Annex II has been updated in accordance. An updated RMP version 6.0 was agreed during the procedure. 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				
IB/0013	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	05/04/2017	n/a		
II/0004	Update of section 5.2 of the SmPC in view of the results of study 20 which was performed to assess the absolute bioavailability and to evaluate the PK parameters of Tagrisso in plasma following a single oral dose and a radio-labelled intravenous (IV) microdoseof[14C] Tagrisso in healthy male subjects. In addition, the MAH took the opportunity to make a minor correction in SmPC section 6.5 and the Package Leaflet, where blister strips have been amended to blisters. Further, an updated RMP version 5.0 was agreed during the procedure.	26/01/2017	22/03/2017	SmPC and PL	The absolute bioavailability of TAGRISSO is 70% (90%CI 67, 73). In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5. However, with current available data, alternative metabolic pathways cannot be fully ruled out.In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5. However, with current available data, alternative metabolic pathways cannot be fully ruled out.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0007	Renewal of the marketing authorisation.	13/10/2016	12/12/2016		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 TAGRISSO, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
PSUSA/10472 /201605	Periodic Safety Update EU Single assessment - osimertinib	01/12/2016	n/a		PRAC Recommendation - maintenance
IB/0011	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	17/11/2016	22/03/2017	SmPC	
IAIN/0008/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	22/09/2016	n/a		

II/0003	Update of section 5.3 of the SmPC to reflect the results of a female rat fertility and early embryonic development study (Study No. 497280). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	12/12/2016	SmPC	Based on studies in animals, female fertility may be impaired by treatment with osimertinib. In a female fertility study in rats, administration of osimertinib at 20 mg/kg/day (approximately equal to the recommended daily clinical dose of 80 mg) had no effects on oestrus cycling or the number of females becoming pregnant, but caused early embryonic deaths. These findings showed evidence of reversibility following a 1 month off-dose.
IB/0005/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.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	17/08/2016	n/a		
IB/0002	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	08/07/2016	12/12/2016	SmPC and Labelling	
IB/0001/G	This was an application for a group of variations. 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 B.II.e.5.a.2 - Change in pack size of the finished	11/03/2016	12/12/2016	SmPC, Labelling and PL	

	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				