GIOTRIF

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/0041	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/06/2023		SmPC, Annex II, Labelling and PL	
IA/0040	A.7 - Administrative change - Deletion of manufacturing sites	22/06/2022	n/a		

[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).

IB/0038	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/06/2021	n/a		
PSUSA/10054 /202009	Periodic Safety Update EU Single assessment - afatinib	10/06/2021	n/a		PRAC Recommendation - maintenance
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/04/2021	13/12/2021	PL	
IA/0035/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 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	07/12/2020	n/a		

IAIN/0034/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.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	08/10/2020		Annex II and PL	
IA/0033/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites	12/03/2020	n/a		
IA/0032	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	06/03/2020	n/a		
II/0031	Update of sections 4.4 and 4.8 of the SmPC in order to introduce a warning and to add gastrointestinal (GI) perforation as an additional adverse drug reaction based on summaries of clinical trial and post-marketing safety data, respectively. The Package Leaflet and the RMP (finally agreed version 8.1) are updated accordingly. The RMP also includes	28/11/2019		SmPC and PL	Gastrointestinal perforation, including fatalities, has been reported during treatment with GIOTRIF in 0.2% of patients across all randomized controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of

	the update of the RMP due to the GVP revision 2 template. In addition, the MAH took the opportunity to update the list of the 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				gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking GIOTRIF, treatment should be permanently discontinued.
IA/0030/G	This was an application for a group of variations. 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) 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 control/testing takes place	10/12/2018	n/a		
IA/0029/G	This was an application for a group of variations. B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/07/2018	n/a		

	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0028	Update of section 5.1 of the SmPC in order to update the efficacy section with data in EGFR TKI-naïve NSCLC patients whose tumours harbour uncommon EGFR mutations based on a meta-analysis across three trials (1200.22, 1200.32 and 1200.34). In addition, the Marketing authorisation holder (MAH) took the opportunity to implement minor linguistic amendments to the translations of the product information annexes: BG, CS, DE, DK, FI, IS, IT, NO, PT, SE and SK. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/06/2018	06/06/2019	SmPC	In three clinical trials of GIOTRIF with prospective tumour genotyping (Phase 3 trials LUX-Lung 3 and -6, and single arm Phase 2 trial LUX-Lung 2), an analysis was conducted of data from a total of 75 TKI-naïve patients with advanced (stage IIIb–IV) lung adenocarcinomas harbouring uncommon EGFR mutations, which were defined as all mutations other than Del 19 and L858R mutations. Patients were treated with GIOTRIF 40 mg (all three trials) or 50 mg (LUX-Lung 2) orally once daily. In patients with tumours harbouring either G719X (N=18), L861Q (N=16), or S768I substitution mutation (N=8), the confirmed ORR was 72.2%, 56.3%, 75.0%, respectively, and the median duration of response was 13.2 months, 12.9 months and 26.3 months, respectively. In patients with tumours harbouring exon 20 insertions (N=23) the confirmed ORR was 8.7% and the median duration of response was 7.1 months. In patients with tumours harbouring de-novo T790M mutations (N=14) the confirmed ORR was 14.3% and the median duration of response was 8.3 months.
R/0026	Renewal of the marketing authorisation.	22/03/2018	16/05/2018	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Giotrif in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.

PSUSA/10054 /201709	Periodic Safety Update EU Single assessment - afatinib	12/04/2018	n/a		PRAC Recommendation - maintenance
II/0025	Submission of the final report from study 1200.217 listed as a category 3 study in the RMP. This is a phase IV study to assess the efficacy and safety of afatinib as second-line therapy for patients with locally advanced or metastatic non-small cell lung cancer harbouring an EGFR mutation who have failed first-line treatment with platinum-based chemotherapy. Risk Management Plan (version 6.0) has been updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/01/2018	n/a		The final analysis report with data from study 1200.217 does not indicate a relevantly different adverse event profile for afatinib in second-line treatment, as compared with first-line treatment. Therefore no amendment to the product information was warranted based on these data.
II/0023	Update of section 4.8 of the SmPC in order to add the adverse reaction nail disorders with a frequency common based on the results of study 1200.131 and supportive evidence from EGFR TKJ comparator studies. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to make some editorial changes to the polish product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/07/2017	23/10/2017	SmPC, Labelling and PL	The randomized, double-blind, placebo-controlled, phase III study (1200.131) designed to evaluate the efficacy and safety of afatinib as adjuvant therapy after chemo-radiotherapy in primary unresected patients with advanced head and neck squamous cell carcinoma showed a higher incidence of non-infectious nail disorders among afatinib treated patients. In addition, there are reasonable mechanistic explanations for this finding with epidermal growth factor receptor (EGFR) function blockade affecting not only the skin, but also skin adnexa. Therefore, based on the available evidence, the section 4.8 of the SmPC is updated to include the adverse reaction nail disorders with a frequency common. The package leaflet is updated accordingly.

IB/0024/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 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 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.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) A.5.b - Administrative change - Change in the name	16/06/2017	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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) 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) A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - 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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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				
PSUSA/10054 /201609	Periodic Safety Update EU Single assessment - afatinib	06/04/2017	n/a		PRAC Recommendation - maintenance
II/0022	Update of section 5.1 of the SmPC in order to update the information about the major mechanism of acquired resistance to afatinib. In addition, the Marketing authorisation holder (MAH) took the opportunity to add the side effects 'itching' and 'dry skin' with frequency very common to the package leaflet to bring it in line with the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/02/2017	23/10/2017	SmPC and PL	Limited non clinical and/or clinical activity was observed in NSCLC tumours with insertion mutations in exon 20. The acquisition of a secondary T790M mutation is a major mechanism of acquired resistance to afatinib and gene dosage of the T790M-containing allele correlates with the degree of resistance in vitro. The T790M mutation is found in approximately 50% of patients' tumours upon disease progression on afatinib, for which T790M targeted EGFR TKIs may be considered as a next line treatment option. Other potential mechanisms of resistance to afatinib have been suggested preclinically and MET gene amplification has been observed clinically.
II/0017	Update of sections 4.2 and 5.2 of the SmPC in order to update the information regarding renal impairment, which has been introduced following completing of the Phase I study 1200.2016. The Package Leaflet is updated accordingly.	13/10/2016	14/11/2016	SmPC, Labelling and PL	During clinical trials, cancer patients with severe renal impairment (creatinine clearance of <29 mL/min/1.73m²) were not included and therefore treatment with afatinib in this population has not been recommended to date. The Phase I study 1200.216 (Pharmacokinetics, safety and

	In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes in the SmPC and to update the labelling (Annex IIIA) in line with 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				tolerability after single dose administration of afatinib in moderate and severe renal impairment in comparison to subjects with normal renal function) aimed to allow such patients to receive treatment with afatinib by developing dosing recommendations, in accordance with FDA postmarketing requirements. The trial was also expected to confirm whether adjustment of the starting dose of afatinib in patients with moderate or several renal impairment is required. In the study, exposure to afatinib was found to be increased in patients with moderate or severe renal impairment. Based on this trial and population pharmacokinetic analysis of data derived from clinical trials in various tumour types, it is concluded that adjustment to the starting dose in patients with mild, moderate or severe renal impairment are not necessary, but patients with severe renal impairment should be monitored and the dose adjusted if not tolerated. Treatment of patients with eGFR <15 ml/min/1.73m2 or on dialysis has not been studied and therefore treatment with afatinib is not recommended for these patients. Therefore, the sections 4.2 and 5.2 of the SmPC have been updated to include the above recommendation regarding renal impairment. The Package Leaflet is updated accordingly.
II/0020	Update of section 4.8 of the SmPC in order to include a table comparing adverse drug reactions (with frequency very common) observed in the global, randomised, open-label, Phase IIb trial (LUX-Lung 7) with afatinib and gefitinib and update of section 5.1 of the SmPC in order to add the results of the primary analysis of this study.	10/11/2016	23/10/2017	SmPC	LUX-Lung 7 is a randomised, global, open label Phase IIb trial investigating the efficacy and safety of Giotrif (afatinib) in patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations in the first-line setting. As the results of the primary analyses of this study have become available, the product information is being updated. The section 4.8 of the

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				summary of product characteristics (SmPC) is updated to include a table comparing adverse drug reactions (with frequency very common) observed in the study LUX-Lung 7 with afatinib and gefitinib. The clinical trial section (5.1) of the SmPC is updated to include the results of the primary analyses of the primary endpoints, progression free survival (PFS), time to treatment failure (TTF) and overall survival (OS) of this study.
PSUSA/10054 /201603	Periodic Safety Update EU Single assessment - afatinib	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0019	Update of section 4.4 of the SmPC in order to add toxic epidermal necrolysis to the existing warning on skin related adverse events and update of section 4.8 of the SmPC to add toxic epidermal necrolysis/Stevens Johnson syndrome as a frequency rare, based on post-marketing experience. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to place the required safety features on the packaging (i.e. Unique Identifier – 2D Barcode and Human Readable Data) in line with the latest QRD template version 10. The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	14/11/2016	SmPC, Labelling and PL	A cumulative review of the clinical trial safety database for afatinib showed that the frequency of the reported Stevens Johnson Syndrome (SJS) events in clinical trials is < 0.1%, based on two SJS cases reported with afatinib. A search of the MAH global safety database retrieved 12 cases for SJS/ toxic epidermal necrolysis (TEN) where a causal association could not be ruled out. Based on these post-marketing reports, the section 4.4 of the SmPC of Giotrif is updated to add toxic epidermal necrolysis to the existing warning on skin related adverse events. Section 4.8 of the SmPC is also updated to add TEN and SJS with a frequency category of rare.

PSUSA/10054 /201509	Periodic Safety Update EU Single assessment - afatinib	14/04/2016	n/a		PRAC Recommendation - maintenance
II/0012	Extension of indications to include patients with locally advanced or metastatic Non-small cell lung cancer (NSCLC) of squamous histology progressing on or after platinum-based chemotherapy. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/02/2016	31/03/2016	SmPC, Annex II and PL	Please refer to the published Assessment Report Giotrif H-2280-II-12-AR.
II/0015	Update of section 4.8 of the SmPC to add the new adverse reaction pancreatitis; the Package Leaflet has been updated accordingly. Furthermore, the MAH has implemented the latest QRD template, version 9.1, by amending the PSUR standard statement in Annex II as well as by introducing a combined SmPC for all four approved product strengths. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	31/03/2016	SmPC, Annex II and PL	
PSUSA/10054 /201503	Periodic Safety Update EU Single assessment - afatinib	08/10/2015	n/a		PRAC Recommendation - maintenance
II/0014	Update of sections 4.6 and 5.2 of the SmPC in order to update the pharmacokinetic information based on results from PK sub-study in patients treated for 6 months or longer. In addition, editorial changes have	24/09/2015	31/03/2016	SmPC	

	been proposed in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0013	Update of section 4.8 of the SmPC in order to add nausea and vomiting with the frequency very common based on clinical data from the Phase III trial LUX-Lung 8 (Trial 1200.125). The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	31/03/2016	SmPC and PL	
IB/0011	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/08/2015	n/a		
II/0009	Update of section 5.1 of the SmPC in order to amend the clinical trial section of the SmPC by updated overall survival (OS) data from the pivotal Phase Ill trial LUX-Lung 3. The MAH made a correction of a typo error in Annex II. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Spanish and Portuguese local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to	23/07/2015	31/03/2016	SmPC, Annex II and PL	Updated Overall Survival data on the use of afatinib have been introduced in the product information after analysis of clinical data.

	new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10054 /201409	Periodic Safety Update EU Single assessment - afatinib	10/04/2015	n/a		PRAC Recommendation - maintenance
IA/0007	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/12/2014	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/10/2014	31/03/2016	PL	
PSUV/0004	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IA/0005	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	25/09/2014	n/a		
IG/0432	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/04/2014	n/a		
IAIN/0001	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/12/2013	n/a		