Tafinlar

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
IAIN/0075/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	04/12/2024		Annex II and PL	

[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).

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IG/1769	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	07/08/2024		SmPC and PL	
WS/2647	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4, 4.8, and 5.1 of the SmPC for Tafinlar and section 5.1 of the SmPC for Mekinist in order to update efficacy and safety information based on final results from study CDRB436F2301 (COMBI-AD); this is a phase 3 randomized double blind study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection. The RMP version 11.1 for Tafinlar and version 19.2 for Mekinist have also been submitted. In addition, MAH took the opportunity to introduce minor editorial changes to the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/07/2024		SmPC	SmPC new text "During the long term (up to 10 years) off treatment follow-up, 2 additional patients reported cuSCC in each treatment arm." See Tafinlar SmPC Section 4.4 Efficacy results from study BRF115532 (COMBI-AD): "At the time of the final OS analysis, the median duration of follow-up was 8.3 years in the combination arm and 6.9 years in the placebo arm. The observed difference in OS was not statistically significant (HR: 0.80; 95% CI: 0.62, 1.01) with 125 events (29%) in the combination arm and 136 events (31%) in the placebo arm. Estimated 5-year OS rates were 79% in the combination arm and 70% in the placebo arm, and estimated 10-year OS rates were 66% in the combination arm and 63% in the placebo arm." See Tafinlar and Mekinist SmPCs, Section 5.1

IAIN/0072/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites	19/06/2024		Annex II and PL	
WS/2685	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	30/05/2024		SmPC	
WS/2671	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to add 'Atrioventricular (AV) block' with an uncommon frequency for Finlee and Spexotras and common frequency for Tafinlar to the list of adverse drug reactions (ADRs), following the PRAC recommendation in the PSUR for Mekinist (PSUSA/00010262/202305). The Package Leaflet is updated accordingly.	16/05/2024		SmPC and PL	Not applicable For more information, please refer to the Summary of Product Characteristics.

	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
IB/0069/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 variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition 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.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	08/05/2024	n/a		
WS/2612	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/04/2024		SmPC and PL	SmPC new text Tumour lysis syndrome The occurrence of TLS, which may be fatal, has been associated with the use of dabrafenib in combination with

	Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on Tumour lysis syndrome and add Tumour lysis syndrome to the list of adverse drug reactions (ADRs) with frequency Not known based on the review of MAH global database, clinical trials database and literature. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.3 and to introduce editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				trametinib (see section 4.8). Risk factors for TLS include high tumour burden, pre existing chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. Patients with risk factors for TLS should be closely monitored and prophylactic hydration should be considered. TLS should be treated promptly, as clinically indicated. For more information, please refer to the Summary of Product Characteristics.
IAIN/0068	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	13/03/2024	n/a		
IG/1710	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	07/03/2024		SmPC and PL	
IAIN/0064	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/01/2024	n/a		
IA/0063	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	04/12/2023	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IAIN/0062/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) 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	16/08/2023	01/02/2024	Annex II and PL	
IB/0061	B.II.c.z - Change in control of excipients in the Finished Product - Other variation	25/07/2023	n/a		
IB/0060	B.II.d.z - Change in control of the Finished Product - Other variation	07/07/2023	n/a		
PSUSA/10084 /202208	Periodic Safety Update EU Single assessment - dabrafenib	14/04/2023	n/a		PRAC Recommendation - maintenance
IAIN/0059	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/02/2023	01/02/2024	SmPC and PL	To update sections 4.4 and 4.8 of the SmPC and sections 2 and 4 of the PL to implement the signal recommendations on `Dabrafenib; trametinib – Haemophagocytic lymphohistiocytosis' (EPITT no: 19824), adopted at the 12 Jan 2023 PRAC meeting.
IB/0057/G	This was an application for a group of variations.	03/11/2022	n/a		

	B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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 A.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0056	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/06/2022	n/a		
WS/2114	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC with the final efficacy data from Study BRF113928	11/11/2021	31/10/2022	SmPC	SmPC new text: At the final analysis of efficacy performed 5 years after last subject first dose (data cut-off 7 January 2021), the primary endpoint of investigator assessed ORR was 63.9% (95% CI, 46.2%, 79.2%) in the first line population and 68.4% (95% CI, 54.8%, 80.1%) in the previously treated

	(CDRB436E2201), conducted in patients with stage IV BRAF V600 mutant NSCLC, in fulfilment of a post-authorisation measure (REC) from the initial MA. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				population. For more information, please refer to the Summary of Product Characteristics.
IB/0055/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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	13/10/2021	n/a		
WS/2070	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the recommendations for the management of pyrexia and to reflect the results of	22/07/2021	26/08/2021	SmPC, Annex II, Labelling and PL	A comparison of five large clinical studies showed that a revised guidance for the management of pyrexia resulted in a reduction in the incidence of grade 3/4 pyrexia AEs, hospitalizations due to serious pyrexia, and pyrexia with complications. Based on this comparison, it is recommended that therapy should be interrupted (trametinib when used as monotherapy, and both

	cross comparison clinical studies that used either the existing or updated pyrexia management guidance; the Package Leaflets are updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives and to include minor editorial changes in the Package Leaflets. The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, and Package Leaflet. Amendments are also made to Annex II and Annex IIIA of Tafinlar product information to bring it in line with the QRD template version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				trametinib and dabrafenib when used in combination; dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination) if a patient's temperature is ≥38oC. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice. Trametinib, dabrafenib or both trametinib and dabrafenib, when used in combination, should be restarted if the patient is symptom free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. For more information, please refer to the Summary of Product Characteristics.
IA/0053/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.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	04/08/2021	n/a		

WS/2008/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 Update of section 5.1 of the Mekinist (trametinib) and Tafinlar (dabrafenib) SmPC to include the 5-years efficacy results from study Phase III study COMBI-AD. This is a two-arm, randomized, double-blind Phase III study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of melanoma after surgical resection in adult patients with a BRAF V600 mutation. Type IA A.6 update of the SmPC with the updated ATC codes released by WHO A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/06/2021	26/08/2021	SmPC	Based on updated data from Phase III study COMBI-AD with an additional 29 months of follow-up compared to the primary analysis (minimum follow-up of 59 months), the recurrence-free survival benefit was maintained with an estimated HR of 0.51 (95% CI: (0.42, 0.61). The 5-year RFS rate was 52% (95% CI: 48, 58) in the combination arm compared to 36% (95% CI: 32, 41) in the placebo arm. For more information, please refer to the Summary of Product Characteristics.
II/0049	Submission of the final report from study 201710 listed as a category 3 study in the RMP. This is a study to perform evaluation of secondary malignancies in patients treated with dabrafenib in randomized, controlled trials. RMP version 10.1 had also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	11/03/2021	n/a		

	of studies to the competent authority				
IAIN/0050	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/01/2021	26/08/2021	SmPC and PL	
IA/0048/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	16/12/2020	n/a		
IAIN/0047	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	08/12/2020	26/08/2021	Annex II and PL	
II/0046	Submission of the final report from study DRB436A2106 listed as a category 3 study in the RMP. This is a phase I, open label, multicenter, single dose study to evaluate the pharmacokinetics of dabrafenib in healthy subjects with normal renal function and subjects with impaired renal function. C.I.13 - Other variations not specifically covered	16/07/2020	n/a		Not applicable

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0045	Submission of the final report from study DRB436A2107 listed as a category 3 study in the RMP. This is a phase I, open label, multicenter, single dose study to evaluate the pharmacokinetics of dabrafenib in healthy subjects with normal hepatic function and subjects with impaired hepatic function. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/07/2020	n/a		Not applicable.
PSUSA/10084 /201908	Periodic Safety Update EU Single assessment - dabrafenib	12/03/2020	n/a		PRAC Recommendation - maintenance
IAIN/0044/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) A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	04/12/2019	n/a		

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
WS/1636/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the Mekinist (trametinib) and Tafinlar (dabrafenib) SmPC to include the 5-years overall survival (OS) results from study MEK115306 (COMBI-d), a phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable or metastatic BRAF V600/K mutation-positive cutaneous melanoma and the 5-years overall survival (OS) results from study MEK116513 (COMBI-v), a phase III, open-label, 2 arm, randomised study comparing dabrafenib and trametinib combination therapy with	21/11/2019	04/05/2020	SmPC	From an OS analysis of study MEK115306 (COMBI-d) at 5 years, the median OS for the combination arm was approximately 7 months longer than for dabrafenib monotherapy (25.8 months versus 18.7 months) with 5-year survival rates of 32% for the combination versus 27% for dabrafenib monotherapy. The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years. The 5-year overall survival rate was 40% (95% CI: 31.2, 48.4) in the combination arm versus 33% (95% CI: 25.0, 41.0) in the dabrafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 8.4, 26.0) in the combination arm versus 14% (95% CI: 6.8, 23.1) in the dabrafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline. From an OS analysis of study MEK116513 (COMBI-v) at 5 years, the median OS for the combination arm was approximately 8 months longer than the median OS for

	vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma. 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				vemurafenib monotherapy (26.0 months versus 17.8 months) with 5-year survival rates of 36% for the combination versus 23% for vemurafenib monotherapy (Table 8, Figure 2). The Kaplan-Meier OS curve appears to stabilise from 3 to 5 years (see Figure 2). The 5-year overall survival rate was 46% (95% CI: 38.8, 52.0) in the combination arm versus 28% (95% CI: 22.5, 34.6) in the vemurafenib monotherapy arm for patients who had a normal lactate dehydrogenase level at baseline, and 16% (95% CI: 9.3, 23.3) in the combination arm versus 10% (95% CI: 5.1, 17.4) in the vemurafenib monotherapy arm for patients with an elevated lactate dehydrogenase level at baseline. For more information please refer to the Summary of Product Characteristics.
IA/0041/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.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	27/09/2019	n/a		
PSUSA/10084 /201808	Periodic Safety Update EU Single assessment - dabrafenib	28/03/2019	27/05/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10084/201808.
II/0038	Update of section 4.6 of the SmPC in order to update information on fertility, pregnancy and lactation after	16/05/2019	04/05/2020	SmPC and PL	

	routine review of the company core data sheet, taking into consideration the original source documentation from GSK (former MAH), current scientific knowledge, published literature, as well as health authority and working group guidelines. The Package leaflet is being updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to include some editorial changes in section 4.4 and 4.8 of the SmPC and in section 4 of the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0039/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 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.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	20/02/2019	27/05/2019	SmPC, Labelling and PL	

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms 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.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				
WS/1468	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to reflect study results from study BRF117277, a Phase II, Open-Label, Multicentre Study of Dabrafenib plus Trametinib in Subjects with BRAF Mutation- Positive Melanoma that has Metastasized to the Brain (COMBI-MB). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	14/02/2019	27/05/2019	SmPC	The safety and efficacy of the combination of trametinib and dabrafenib have been evaluated in a multi-cohort, open-label, Phase II study in patients with BRAF V600 mutant melanoma with brain metastases. A total of 125 patients were enrolled into four cohorts. The primary endpoint of the study was intracranial response in Cohort A defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. This cohort included patients with BRAFV600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1. The intracranial

	data				response rate in 76 patients in cohort A was 59% (95% CI: 47.3-70.4). Due to small sample size reflected by wide 95% CIs, the results in cohorts B, C, and D should be interpreted with caution. The safety profile observed in the study appears to be consistent with the integrated safety profile of the combination. For more information please refer to the Summary of Product Characteristics.
IB/0036/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 B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a	04/01/2019	n/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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.c.1.z - Change in immediate packaging of the AS - Other variation 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				
WS/1274	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the Mekinist and Tafinlar SmPCs are updated. The Package Leaflet and the Risk Management plan (version 14.1 for Mekinist and version 9.1 for Tafinlar, according to GVP module V revision 2) are updated in accordance. In addition, the Worksharing applicant (WSA) took the opportunity to correct some typos throughout the Mekinist and Tafinlar	26/07/2018	27/08/2018	SmPC and PL	Please refer to the published assessment report Mekinist-Tafinlar-WS-1274: EPAR - Assessment Report – Variation

	product information, to include a cross reference to the Mekinist SmPC in section 4.6 of the Tafinlar SmPC regarding fertility, to update the list of local representatives for Bulgaria, Hungary, Estonia, Latvia and Lithuania in the Package Leaflet of both products. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
T/0032	Transfer of Marketing Authorisation	01/06/2018	06/07/2018	SmPC, Labelling and PL	
IG/0950	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)	18/06/2018	n/a		
R/0030	Renewal of the marketing authorisation.	22/02/2018	08/05/2018	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 Tafinlar in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10084 /201708	Periodic Safety Update EU Single assessment - dabrafenib	08/03/2018	n/a		PRAC Recommendation - maintenance
WS/1210/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/01/2018	08/05/2018	SmPC	An updated OS analysis (15 February 2016) for study MEK115306 (COMBI-d) demonstrated an improvement in OS for the combination compared with dabrafenib monotherapy. The 3-year OS estimate for the combination

	Update of section 5.1 of the Mekinist (trametinib) and Tafinlar (dabrafenib) SmPC to include the 3-years overall survival (OS) results from study MEK115306 (COMBI-d), a phase III, randomised, double-blinded study comparing the combination of dabrafenib and trametinib to dabrafenib and placebo in first-line therapy for subjects with unresectable or metastatic BRAF V600/K mutation-positive cutaneous melanoma. Update of section 5.1 of the Mekinist (trametinib) and Tafinlar (dabrafenib) SmPC to include the 3-years overall survival (OS) results from study MEK116513 (COMBI-v), a phase III, open-label, 2 arm, randomised study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma. In addition the MAH has taken the opportunity to align the storage recommendations in section 5 of the Package Leaflet with the current wording in section 6.4 of the SmPC for Mekinist. 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				arm was greater than for dabrafenib monotherapy (44% vs. 32%, respectively). The median OS for the combination arm was approximately 8 months longer than the median OS for dabrafenib monotherapy (26.7 months versus 18.7 months). These data also demonstrated a reduction in the risk of death (HR=0.75, 95% CI: 0.58, 0.96) which was consistent with the primary OS analysis. An updated OS analysis (15 July 2016) for study MEK116513 (COMBI-v) demonstrated improvement in OS for the combination compared with vemurafenib monotherapy. The 3-year OS estimate was 45% for combination therapy and 31% for vemurafenib. The median OS for the combination arm was approximately 8 months longer than the median OS for vemurafenib monotherapy (26.1 months versus 17.8 months). These data also demonstrated a reduction in the risk of death (HR=0.68, 95% CI: 0.56, 0.83) which was consistent with the primary OS analysis. These updated 3-year OS data for these two phase III studies demonstrated that durable survival is achievable with dabrafenib and trametinib, that the beneficial effect of combining dabrafenib with trametinib is maintained over time and that long-term clinical tolerability is considered acceptable.
II/0029	Update of section 5.2 of the SmPC in order to update the information on the in vitro evaluation of drug-	18/01/2018	08/05/2018	SmPC	In vitro studies were performed to test dabrafenib as a substrate of the human BCRP transporter (study

	drug interaction potential (to include that dabrafenib is a human BCRP substrate and a OCT2 inhibitor but that the risk of a drug drug interaction is minimal with substrates of OAT1, OAT3 and OTC2 based on clinical exposure of dabrafenib and its metabolites), based on the results of non-clinical studies 2014N220059 and 2015N235499. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				2015N235499) and inhibition of the human OCT2 transporter by dabrafenib and its major metabolites (study 2014N220059). The results of study 2015N235499 demonstrated that dabrafenib is also a substrate of human BCRP in vitro. The results of study 2014N220059 demonstrated that dabrafenib and its desmethyl metabolite were found to be inhibitors of organic cation transporter 2 (OCT2) in vitro, the risk of a drug drug interaction at these transporters is minimal based on clinical exposure of dabrafenib and its metabolites.
II/0027	Submission of the final report from study BRF113683 (BREAK-3) listed as a category 3 study in the RMP. This is a phase III, randomised, two-arm, open label study comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF mutation positive advanced (stage III) or metastatic (stage IV) melanoma. This study is aimed to confirm the superior efficacy of dabrafenib compared to DTIC. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/12/2017	n/a		The final report from study BRF113683 (BREAK-3), a phase III, randomised, two-arm, open label study comparing dabrafenib to dacarbazine (DTIC) in previously untreated patients with BRAF mutation positive advanced (stage III) or metastatic (stage IV) melanoma to confirm the superior efficacy of dabrafenib compared to DTIC provided further information on the efficacy comparison between dabrafenib and DTIC. The final results from this study compared with the preliminary results available at time of the initial Marketing Authorisation application did not identify any significant difference between primary and secondary efficacy endpoints (progression free survival and overall survival respectively) nor any clinically significant changes in the safety profile. Overall, the results presented in this application are consistent with previous reported data and did not warrant amendment to the product information.
II/0025	Update of sections 4.4, 4.5 and 5.2 of the SmPC to include the results of a drug-drug interaction between dabrafenib and rosuvastatin (an	05/10/2017	08/05/2018	SmPC	The results of a drug-drug interaction study (200919) between dabrafenib and rosuvastatin showed that Cmax of rosuvastatin increased 2.6-fold whereas the area under the

	OATP1B1/1B3 substrate) and between dabrafenib and midazolam (a CYP3A4 substrate) based on study 200919; this is a phase I open-label fixed sequence study to evaluate the effects of an OATP1B1/1B3 substrate (rosuvastatin) and of a CYP3A4 substrate (midazolam) on the repeat dose pharmacokinetics of dabrafenib in subjects with BRAFV60 mutation positive tumours, in fulfillment of MEA 001. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				curve (AUC) was only minimally changed (7% increase). The increased Cmax of rosuvastatin is unlikely to have clinical relevance. Sections 4.4, 4.5 and 5.2 of the SmPC for Tafinlar has been updated with this information.
II/0024	Update of section 4.5 of the SmPC in order to include the results of a drug-drug interaction between dabrafenib and rifampicin (a CYP3A4/CYP2C8 inducer) and between dabrafenib and rabeprazole based on the final results of study 200072, a phase I open-label fixed sequence study to evaluate the effects of potent CYP3A4 inducer (rifampicin) and of a pH elevating agent (rabeprazole) on the repeat dose pharmacokinetics of dabrafenib in subjects with BRAFV60 mutation positive tumours, to fulfil MEA 005. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/07/2017	08/05/2018	SmPC	Result from study 200072 showed that administration of rifampin (a CYP3A4/CYP2C8 inducer) 600 mg once daily with dabrafenib 150 mg twice daily resulted in a decrease in repeat dose dabrafenib Cmax (27%) and AUC (34%). No relevant change in AUC was noted for hydroxy-dabrafenib. There was an increase in AUC of 73% for carboxy dabrafenib and a decrease in AUC of 30% for desmethyl dabrafenib. Co administration of repeat doses of dabrafenib 150 mg twice daily and the pH elevating agent rabeprazole 40 mg once daily resulted in a 3% increase in AUC and a 12% decrease in dabrafenib Cmax. These changes in dabrafenib AUC and Cmax are considered not clinically meaningful. Medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g. proton pump inhibitors, H2 receptor antagonists, antacids) are not expected to reduce the bioavailability of dabrafenib.
PSUSA/10084 /201608	Periodic Safety Update EU Single assessment - dabrafenib	23/03/2017	24/05/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10084/201608.
WS/0996	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include the combination treatment with trametinib and dabrafenib of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the Mekinist and Tafinlar SmPC are updated. The Package Leaflet and RMP are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to align the SmPCs of Mekinist and Tafinlar. Furthermore, the Product Information is brought in line with the latest QRD template version 10. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/02/2017	29/03/2017	SmPC, Labelling and PL	
IA/0021/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	01/07/2016	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				
II/0019	Update of SmPC sections 4.2, 4.4, 4.8 and 5.1 based on the final study report from Study BRF113773, which was undertaken to assess the QTcF interval prolongation potential of dabrafenib in order to fulfil the post-approval measure (PAM) MEA 002. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/05/2016	29/03/2017	SmPC	Worst-case QTc prolongation of >60 millisecond (msec) was observed in 3% of dabrafenib-treated subjects (one >500 msec in the integrated safety population). In the Phase III study MEK115306 no patients treated with trametinib in combination with dabrafenib had worst-case QTcB prolongation to >500 msec; QTcB was increased more than 60 msec from baseline in 1% (3/209) of patients. In the Phase III study MEK116513 four patients (1%) treated with trametinib in combination with dabrafenib had a QTcB Grade 3 increase (>500 msec). Two of these patients had a QTcB Grade 3 increase (>500 msec) that was also an increase >60 msec from baseline. The potential effect of dabrafenib on QT prolongation was assessed in a dedicated multiple dose QT study. A supratherapeutic dose of 300 mg dabrafenib twice daily was administered in 32 subjects with BRAF V600 mutation-positive tumours. No clinically relevant effect of dabrafenib or its metabolites on the QTc interval was observed.
IAIN/0020/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	11/05/2016	n/a		

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II/0018	Update of section 4.8 of the SmPC for the inclusion of "Bradycardia" and "Heart rate decreased" to reflect the known safety profile of dabrafenib when used in combination with trametinib. Additionally, the acronyms 'BID' and 'QD' have been replaced with 'twice daily' and 'once daily', respectively and section 4.2 of the SmPC has also been updated for the third recommended dose reduction. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the 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	01/04/2016	02/05/2016	SmPC, Annex II, Labelling and PL	

PSUSA/10084 /201508	Periodic Safety Update EU Single assessment - dabrafenib	17/03/2016	n/a		PRAC Recommendation - maintenance
II/0015/G	This was an application for a group of variations. Update of section 5.3 of the SmPC in order to update preclinical safety data on juvenile toxicity in rats and phototoxicity in mouse on the basis of submitted non clinical studies. 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	08/10/2015	02/05/2016	SmPC	Preclinical safety data indicate that dabrafenib induces earlier vaginal opening without affecting sexual maturity and the effect is considered of little biological relevance; therefore information with regard to these findings is removed from section 5.3 of the SmPC. Dabrafenib was phototoxic in an in vitro mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay and in vivo at doses ≥ 100 mg/kg (> 44 times clinical exposure based on Cmax) in an oral phototoxicity study in hairless mice.
II/0009	Update of section 4.8 of the SmPC in order to reclassify the already listed ADR panniculitis from an immune disorder to a skin and subcutaneous tissue disorder. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	02/05/2016	SmPC	N/A
IB/0016	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/09/2015	n/a		

PSUSA/10084 /201502	Periodic Safety Update EU Single assessment - dabrafenib	10/09/2015	n/a		PRAC Recommendation - maintenance
WS/0736	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to add a new therapeutic indication for the use in combination of trametinib and dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.3 of the SmPC are updated. The Package Leaflet was updated accordingly. Furthermore, an updated RMP version X was approved as part of the application. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/07/2015	25/08/2015	SmPC and PL	Please refer to the sssessment report for EMEA/H/C/WS/0736
IAIN/0014/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer	13/07/2015	25/08/2015	Annex II and PL	

	responsible for importation and/or batch release - Not including batch control/testing				
II/0008	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/06/2015	25/08/2015	SmPC	
T/0010	Marketing Authorisation Transfer from GlaxoSmithKline Trading Services to Novartis Europharm Limited. Transfer of Marketing Authorisation	13/04/2015	06/05/2015	SmPC, Labelling and PL	
IA/0012	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	05/05/2015	n/a		
PSUSA/10084 /201408	Periodic Safety Update EU Single assessment - dabrafenib	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0006	Update of section 5.2 of the SmPC based on data from the non-clinical study 13DMM028 provided to fulfil MEA006 (drug-drug interaction in vitro organic anion transporter polypeptide substrate assay). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/01/2015	06/05/2015	SmPC	Dabrafenib is a substrate of human P-glycoprotein (Pgp) and murine BCRP in vitro. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination and the risk for clinically relevant drug-drug interactions with inhibitors of Pgp or BCRP is low. Dabrafenib is not an in vitro substrate of OATP1B1, OATP1B3 or OATP2B1 transporters.
PSUV/0005	Periodic Safety Update	25/09/2014	21/11/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0005.

II/0001/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	21/11/2014	SmPC and PL	
IG/0442	A.1 - Administrative change - Change in the name and/or address of the MAH	05/06/2014	21/11/2014	SmPC, Labelling and PL	
IB/0003/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.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	06/05/2014	n/a		
II/0002/G	This was an application for a group of variations. Update of section 5.3 with new data from a 26-week toxicology study in mice (G12071). In addition, the MAH revised the submission date for the final report for a drug-drug interaction study (MEA 006) and has updated the RMP accordingly. The MAH also took the opportunity to update the list of local representatives.	20/02/2014	21/11/2014	SmPC and PL	Dabrafenib was administered in a 26-week mouse toxicology study. The toxicity findings were generally similar to what was previously observed in rats and dogs. However, the study showed hepatoxicity as a novel finding in mice. Focal arterial/perivascular inflammation in various tissues was observed in mice and an increased incidence of hepatic arterial degeneration and spontaneous cardiomyocyte degeneration with inflammation (spontaneous cardiomyopathy) was observed in rats (≥0.5

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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				and 0.6 times clinical exposure for rats and mice respectively). Hepatic effects, including hepatocellular necrosis and inflammation, were observed in mice (≥0.6 times clinical exposure).