Mekinist

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/0058	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/02/2023		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.

[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).

IA/0057	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	01/02/2023	n/a		
PSUSA/10262 /202205	Periodic Safety Update EU Single assessment - trametinib	12/01/2023	n/a		PRAC Recommendation - maintenance
II/0053/G	This was an application for a group of variations. B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range 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)	14/07/2022		SmPC, Labelling and PL	The SmPC section 6.3 and 6.4 have been updated with 3-years shelf life and storage conditions 'This medicinal product does not require any special temperature storage conditions.' (to replace 2-years shelf life in a refrigerator). The Labelling and PL have been updated accordingly.
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
II/0051	Update of section 4.2 and 5.2 of the SmPC in order to change posology recommendations in hepatic impairment and update pharmacokinetic information based on final results from study MEC116354 listed as a category 3 study in the RMP; this is a Phase I	24/03/2022	29/04/2022	SmPC	Available data from a clinical pharmacology study (Study XUS23T) indicate a limited impact of moderate to severe hepatic impairment on trametinib exposure. Moreover a population pharmacokinetic analyses and data from the same study in patients with normal hepatic function or with

	Trial of Single Agent Trametinib (GSK1120212) in Advanced Cancer Patients with Hepatic Dysfunction. The RMP version 18 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				mild, moderate or severe bilirubin and/or AST elevations, indicate that hepatic function does not significantly affect trametinib oral clearance. For more information, please refer to the Summary of Product Characteristics.
IA/0054/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	02/02/2022	n/a		
PSUSA/10262 /202105	Periodic Safety Update EU Single assessment - trametinib	13/01/2022	n/a		PRAC Recommendation - maintenance
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 (CDRB436E2201), conducted in patients with stage	11/11/2021	29/04/2022	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 population.

	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				For more information, please refer to the Summary of Product Characteristics.
IA/0052	A.7 - Administrative change - Deletion of manufacturing sites	12/10/2021	n/a		
IB/0048/G	This was an application for a group of variations. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) 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	12/10/2021	29/04/2022	SmPC and PL	

	packaging, for non-sterile medicinal products B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits 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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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 B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation				
WS/2070	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	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,

	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 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				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 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.
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	03/06/2021	23/07/2021	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.

	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				For more information, please refer to the Summary of Product Characteristics.
II/0043	Submission of the final report from study 201711 listed as a category 3 study in the RMP. This is a study to identify and characterize the risk of cardiomyopathy and subsequent sequelae, including safety evaluations of patient populations at highest risk for developing these toxicities. The RMP version 17.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/03/2021	n/a		
IB/0044	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/01/2021	n/a		

II/0041	Update of sections 4.5, 4.6 and 5.2 of the SmPC in order to add drug-drug interaction information with hormonal contraceptives and to updated relevant part of the SmPC regarding this interaction; the Package Leaflet is updated accordingly. Furthermore, the MAH took the occasion to include the information regarding the sodium content in the products in line with relevant guidelines and to bring the PI in line with the QRD template version 10.1. In addition, the MAH took the opportunity to introduce some editorial changes in the PI and to update the list of local representatives for The Netherlands in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/01/2021	23/07/2021	SmPC, Annex II, Labelling and PL	Effects of trametinib on other medicinal products: the effect of repeat-dose trametinib on the steady state pharmacokinetics of combination oral contraceptives, norethindrone and ethinyl estradiol, was assessed in a clinical study that consisted of 19 female patients with solid tumours. Norethindrone exposure increased by 20% and ethinyl estradiol exposure was similar when co-administered with trametinib. Based on these results, no loss of efficacy of hormonal contraceptives is expected when co administered with trametinib monotherapy. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10262 /202005	Periodic Safety Update EU Single assessment - trametinib	14/01/2021	n/a		PRAC Recommendation - maintenance
IAIN/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/01/2021	23/07/2021	SmPC and PL	
IA/0042/G	This was an application for a group of variations. 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 B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished	09/10/2020	n/a		

	product - Other variation				
IAIN/0039	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	23/07/2020	23/07/2021	Annex II and PL	
II/0038/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.7 - Administrative change - Deletion of manufacturing sites 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	14/05/2020	n/a		

	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.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation 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 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.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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification 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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of				

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	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				
PSUSA/10262 /201905	Periodic Safety Update EU Single assessment - trametinib	16/01/2020	n/a		PRAC Recommendation - maintenance
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 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	21/11/2019	04/02/2020	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 (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

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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.
IAIN/0037/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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	29/10/2019	n/a		
II/0033	Update of sections 4.4 and 4.8 of the SmPC to introduce a warning and new ADRs related to severe cutaneous adverse reactions (SCARs) as per request in the outcome of EMEA/H/C/PSUSA/00010084/201808 for Dabrafenib. The Package Leaflet is updated accordingly. In	16/05/2019	04/02/2020	SmPC and PL	Cases of severe cutaneous adverse reactions (SCARs), including Stevens Johnson syndrome, generalised dermatitis exfoliative and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib/trametinib combination therapy. Before

	addition, the Marketing authorisation holder (MAH) took the opportunity to include some editorial changes in sections 4.4, 4.6 and 4.8 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be withdrawn.
IA/0034	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	26/04/2019	n/a		
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 data	14/02/2019	04/02/2020	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 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.
R/0029	Renewal of the marketing authorisation.	13/12/2018	14/02/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Mekinist in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10262 /201805	Periodic Safety Update EU Single assessment - trametinib	17/01/2019	n/a		PRAC Recommendation - maintenance
IB/0031	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/12/2018	n/a		
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 product information, to include a cross reference to	26/07/2018	27/08/2018	SmPC and PL	Please refer to the published assessment report Mekinist-Tafinlar-WS-1274: EPAR - Assessment Report – Variation

	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				
IAIN/0027/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.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.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	30/07/2018	n/a		
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		

T/0025	Transfer of Marketing Authorisation	20/03/2018	12/04/2018	SmPC, Labelling and PL	
IB/0024	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	15/03/2018	n/a		
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. 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	25/01/2018	12/04/2018	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 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

	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				trametinib, that the beneficial effect of combining dabrafenib with trametinib is maintained over time and that long-term clinical tolerability is considered acceptable.
PSUSA/10262 /201705	Periodic Safety Update EU Single assessment - trametinib	11/01/2018	n/a		PRAC Recommendation - maintenance
IB/0022	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)	18/10/2017	12/04/2018	SmPC	
PSUSA/10262 /201611	Periodic Safety Update EU Single assessment - trametinib	22/06/2017	14/08/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10262/201611.
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	23/02/2017	27/03/2017	SmPC, Labelling and PL	

	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				
PSUSA/10262 /201605	Periodic Safety Update EU Single assessment - trametinib	12/01/2017	n/a		PRAC Recommendation - maintenance
PSUSA/10262 /201511	Periodic Safety Update EU Single assessment - trametinib	23/06/2016	16/08/2016	SmPC, Labelling and PL	Please refer to Mekinist- EMEA/H/C/PSUSA/00010262/201511 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IAIN/0016/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 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	11/05/2016	n/a		

	site 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 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 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 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 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 B.II.b.1.a - Replacement or addition of a				

	manufacturing site for the FP - Secondary packaging site				
PSUSA/10262 /201505	Periodic Safety Update EU Single assessment - trametinib	28/01/2016	22/03/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10262/201505.
II/0014	Submission of the final study report for study MEK114655: "Phase I, Single Sequence, Placebo-Controlled, Single-Blind Study to Evaluate the Effect of Repeat Oral Dosing of GSK1120212 on Cardiac Repolarization in Subjects with Solid Tumors" which fulfils MEA007. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/02/2016	n/a		
II/0013	Update of section 4.8 of the SmPC in order to add Bradycardia and Heart rate decreased as ADRs with a common frequency as a result of clinical studies and post marketing reports. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	16/08/2016	SmPC, Annex II, Labelling and PL	

IB/0012	C.I.7.b - Deletion of - a strength	03/12/2015	22/03/2016	SmPC, Labelling and PL	
IAIN/0011/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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	16/10/2015	n/a		
II/0007	Update of sections 4.2 and 5.3 of the SmPC in order to update the safety information based on new preclinical data from an oral juvenile toxicity study in rats. Moreover, the consolidated RMP version 12 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	22/03/2016	SmPC	Studies in juvenile animals have shown adverse effects of trametinib which had not been observed in adult animals. Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately 2 times adult human clinical exposure based on AUC).
II/0006/G	This was an application for a group of variations.	24/09/2015	22/03/2016	SmPC	Trametinib is an in vitro substrate of the efflux transporter

	Update of sections 4.5 and 5.2 of the SmPC in order to update the safety information based on new preclinical data provided to fulfil 4 nonclinical Post-Authorisation Measures (REC 001, MEA 004, MEA 005 and MEA 006). Moreover, the consolidated RMP version 12 has been agreed. 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				P-gp. As it cannot be excluded that strong inhibition of hepatic P-gp may result in increased levels of trametinib, caution is advised when co-administering trametininb with medicinal products that are strong inhibitors of P-gp (e.g. verapamil, cyclosporine, ritonavir, quinidine, itraconazole). In vitro studies demonstrated that trametinib is metabolised predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways. CYP3A4 oxidation is considered a minor pathway of metabolism. The deacetylation is mediated by carboxyl-esterases (i.e. carboxylesterase 1b/c and 2) and may also be mediated by other hydrolytic enzymes. Trametinib was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and CYP2C19, an inducer of CYP3A4 and an inhibitor of the transporters OAT1, OAT3, OCT2, MATE1, OATP1B1, OATP1B3, Pgp and BCRP. However, based on the low dose and low clinical systemic exposure relative to the in vitro potency of inhibition or induction values, trametinib is not considered to be a in vivo inhibitor or inducer of these enzymes or transporters, although transient inhibition of BCRP substrates in the gut may occur. Trametinib is not a substrate of CYP enzymes or of the transporters BCRP, OATP1B1, OATP1B3, OATP2B1, OCT1, MRP2, and MATE1. Trametinib is an in vitro substrate of BSEP and the efflux transporter P-gp. Although tramatinib exposure is unlikely to be affected by inhibition of BSEP, increased levels of trametinib upon strong inhibition of hepatic P-gp cannot be excluded.
WS/0736	This was an application for a variation following a worksharing procedure according to Article 20 of	23/07/2015	25/08/2015	SmPC and PL	Please refer to the sssessment report for

	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				EMEA/H/C/WS/0736
II/0002/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to add warnings regarding Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) and to update the safety information on haemorrhage. The Package Leaflet is being updated to make it in line with the existing pneumonitis information in the SmPC. 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	23/07/2015	25/08/2015	SmPC and PL	Deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur in patients taking trametinib. If patients develop symptoms of DVT or PE they should immediately seek medical care. Haemorrhagic events, including major haemorrhagic events (defined as symptomatic bleeding in a critical area or organ) and fatal intracranial haemorrhages, have occurred in patients taking trametinib. The majority of bleeding events were mild.

IAIN/0009/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 responsible for importation and/or batch release - Not including batch control/testing	13/07/2015	25/08/2015	Annex II and PL	
PSUSA/10262 /201412	Periodic Safety Update EU Single assessment - trametinib	09/07/2015	n/a		PRAC Recommendation - maintenance
II/0003	Update of sections 4.2 and 4.4 of the SmPC in order to remove reference to the specific rash management guidelines. 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	21/05/2015	25/08/2015	SmPC and PL	Deletion of rush management guidance following retrospective analysis of dermatologic adverse reaction which demonstrate that there is no benefit of prophylaxis to prevent dermatologic AEs and there is no information on the success of the treatment of AEs and the dose adjustment (dose reduction or interruption), when they have occurred.
T/0005	Transfer of MArketing Authorisation from Glaxo Group Ltd. to Novartis Europharm Limited. Transfer of Marketing Authorisation	07/04/2015	20/04/2015	SmPC, Labelling and PL	

II/0001/G	This was an application for a group of variations. C.1.4 - To update Section 5.3 (Preclinical Safety Data) of the SmPC following the completion of a trametinib in vitro phototoxicity assay C.1.13 – Submission of the final reports from trametinib and metabolite M5 plasma protein binding studies C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/11/2014	20/04/2015	SmPC	Trametinib was phototoxic in an in vitro mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures, indicating that there is low risk for phototoxicity to patients taking trametinib. M5 is highly bound to plasma proteins with a free fraction of 1.2%, which is comparable to the free fraction of trametinib at clinically relevant concentrations of 1.4%. The calculated contribution of M5 to the total pharmacological activity is 12%. This is less than the recommended cut-off value of 50%. Therefore, it is agreed that the enzyme(s) and transporter(s) involved in the elimination pathway(s) of M5 do not have to be further investigated.