Mektovi

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
WS/2658	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 5.1 of the SmPC in order to update efficacy and safety information following the	14/11/2024		SmPC	SmPC new text The final efficacy analysis was consistent with the results of the interim analysis and showed a benefit in OS for Combo 450 over vemurafenib (HR 0.67 [95% CI:0.53,0.84] with median OS of 33.6 months vs 16.9 months). The PFS and ORR (per BIRC) results also confirmed a numerical benefit

[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).

	outcome of procedures 004579/0000 and R/0024 based on final results from study C4221004 (CMEK162B2301). This was a 2-part, multi-center, randomized, open label, Phase III study comparing the efficacy and safety of encorafenib plus binimetinib to vemurafenib and encorafenib monotherapy in participants with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation. In addition, the MAH took the opportunity to introduce editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				in favour of Combo 450, with a 7.6 months longer median PFS in the Combo 450 arm as compared to vemurafenib arm. Moreover, Part 2 final analysis showed a numerical difference in OS for Combo 300 (Part 2) over Enco 300 monotherapy (Parts 1+2) (HR 0.89 [95% CI:0.72,1.09] with median OS of 27.1 months [95% CI:21.6-33.3] vs 22.7 months [95% CI: 19.3-29.3]). The median PFS remained longer in the Combo 300 (Part 2) arm than in the Enco 300 (Parts 1+2) group with median PFS estimates of 12.9 months (95% CI: 10.9, 14.9) and 9.2 months (95% CI: 7.4, 11.1), respectively. The confirmed ORR (per BIRC) was 67.8% (95% CI: 61.8, 73.5) and 51.4% (95% CI 45.4, 57.4) in the Combo 300 (Part 2) and Enco 300 (Parts 1 + 2) arms, respectively. Similar results were observed per Investigator assessment. For more information, please refer to the Summary of Product Characteristics.
WS/2538	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 binimetinib in combination with encorafenib for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation for MEKTOVI and BRAFTOVI based on results from study PHAROS (Study ARRAY-818-202) at the primary completion date; this is a Phase II, open-label, multicentre, non-comparative study (interventional). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1,	25/07/2024	29/08/2024	SmPC and PL	Please refer to Scientific Discussion 'WS-2538 Braftovi - Mektovi'

	5.2 and 5.3 of the Braftovi SmPC and sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the Mektovi SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of Braftovi and Mektovi RMPs have also been approved. The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0032	B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement	27/08/2024	n/a		
X/0029	Extension application to add a new strength of 45 mg (film-coated tablets). Annex I_2.(c) Change or addition of a new strength/potency	25/04/2024	17/06/2024	SmPC, Labelling and PL	
PSUSA/10717 /202306	Periodic Safety Update EU Single assessment - binimetinib	25/01/2024	21/03/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10717/202306.
II/0027	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/12/2023	n/a		

R/0024	Renewal of the marketing authorisation.	26/04/2023	23/06/2023	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 Mektovi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0025	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/06/2023	n/a		
IA/0026	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	09/06/2023	n/a		
PSUSA/10717 /202206	Periodic Safety Update EU Single assessment - binimetinib	12/01/2023	n/a		PRAC Recommendation - maintenance
IB/0022	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	11/05/2022	n/a		
IB/0021/G	This was an application for a group of variations. 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.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	11/05/2022	n/a		

IAIN/0020	A.1 - Administrative change - Change in the name and/or address of the MAH	24/01/2022	21/06/2022	SmPC, Labelling and PL	
PSUSA/10717 /202106	Periodic Safety Update EU Single assessment - binimetinib	13/01/2022	n/a		PRAC Recommendation - maintenance
IB/0019	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	12/11/2021	n/a		
II/0015	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/10/2021	n/a		
IA/0018	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	09/09/2021	n/a		
IA/0016	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	09/08/2021	21/06/2022	SmPC	
IA/0014	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	24/06/2021	n/a		
IA/0013	A.7 - Administrative change - Deletion of	08/06/2021	21/06/2022	Annex II and	

	manufacturing sites			PL	
IB/0012/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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.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	27/05/2021	n/a		
PSUSA/10717 /202006	Periodic Safety Update EU Single assessment - binimetinib	14/01/2021	n/a		PRAC Recommendation - maintenance
IA/0011	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/10/2020	n/a		
PSUSA/10717 /201912	Periodic Safety Update EU Single assessment - binimetinib	09/07/2020	n/a		PRAC Recommendation - maintenance

IB/0009	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/06/2020	n/a		
WS/1695	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Note: The MAH in the course of the assessment withdrew Mektovi (binimetinib) from the applied indication. Therefore, the extension of indication only concerns the product Braftovi (encorafenib). Extension of indication to include encorafenib in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy, as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 2.0 is acceptable. Furthermore, the PI is brought in line with the latest QRD template version 10.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/04/2020	30/04/2020	SmPC, Annex II and PL	Please refer to Scientific Discussion Braftovi-H-C-4580-WS-1695.
PSUSA/10717 /201906	Periodic Safety Update EU Single assessment - binimetinib	16/01/2020	n/a		PRAC Recommendation - maintenance

IAIN/0005/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.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.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	08/08/2019	24/10/2019	SmPC, Annex II and PL	
PSUSA/10717 /201812	Periodic Safety Update EU Single assessment - binimetinib	11/07/2019	n/a		PRAC Recommendation - maintenance
IAIN/0004	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	07/05/2019	n/a		
II/0002/G	This was an application for a group of variations. 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	28/03/2019	n/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0001	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	30/10/2018	24/10/2019	SmPC, Labelling and PL	