Summary Report of Benefit-Risk Assessment

MEKTOVI FILM-COATED TABLET 15MG

NEW DRUG APPLICATION

Active Ingredient(s)	Binimetinib
Product Registrant	Zuellig Pharma Pte. Ltd.
Product Registration Number	SIN16826P
Application Route	Abridged evaluation
Date of Approval	19 July 2023

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A INTRODUCTION

Mektovi is indicated in combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by a validated test.

The active substance, binimetinib, is an adenosine triphosphate (ATP)-uncompetitive reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation. The inhibition of MEK leads to the inhibition of the phosphorylation of extracellular signal-regulated kinase (ERK) in BRAF-mutated tumour cells thereby inhibiting cell proliferation and viability.

Mektovi is available as film-coated tablet containing 15 mg of binimetinib. Other ingredients in the tablet cores are croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and colloidal anhydrous silica. Ingredients in the film coating include purified water, iron oxide black, iron oxide yellow, macrogol 3350, polyvinyl alcohol, talc and titanium dioxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, binimetinib, is manufactured at Dynamit Nobel GmbH, Leverkusen, Germany and milled at Micronisierungs-Kontor Oberrot, Baden-Wuerttemberg, Germany. The drug product, Mektovi Film-Coated Tablet 15 mg, is manufactured at ALMAC Pharma Services Limited, Craigavon, United Kingdom.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The packaging is double polyethylene bags placed into 120 litres metallic drums. The stability data presented was adequate to support the storage of the drug substance at 30°C, protected from light, with a re-test period of 60 months.

Drug product:

The tablets are manufactured using a direct compression approach followed by film-coating which is considered a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The container closure system is a PVC/PVDC-Aluminium blister, containing 12 tablets per blister, and 7 blisters per carton. The stability data submitted was adequate to support the shelf-life of 36 months when stored at or below 30ºC.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of binimetinib in combination with encorafenib for the treatment of adult patients who have unresectable or metastatic melanoma with a BRAF V600E or V600K mutation was based primarily on one pivotal Phase III study COLUMBUS. This was a randomised, open-label, multicentre study of binimetinib + encorafenib versus vemurafenib or encorafenib monotherapy in patients with locally advanced, unresectable or metastatic (Stage IIIB, IIIC, or IV) BRAF V600E or V600K mutant melanoma.

The study had two parts. In Part 1, the patients were randomised equally to receive binimetinib 45 mg twice daily + encorafenib 450 mg once daily (Combo 450), encorafenib monotherapy 300 mg once daily or vemurafenib monotherapy 960 mg twice daily. Vemurafenib was the standard of care at the time of the study conduct for the treatment of patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutation. Hence, the use of vemurafenib as an active comparator was considered acceptable. In Part 2, designed to assess the contribution of binimetinib when combined to encorafenib, the patients were randomised in a 3:1 ratio to receive binimetinib 45 mg twice daily + encorafenib 300 mg once daily (Combo 300) or encorafenib 300 mg monotherapy once daily. Patients were treated until progressive disease, unacceptable toxicity, withdrawal of consent, death, physician decision or early termination of the study.

The primary endpoint was progression-free survival (PFS), defined as the time from the date of randomisation to the date of the first documented progression based on tumour assessment read centrally by a blinded independent review committee (BIRC) according to RECIST v1.1 criteria, or death due to any cause, whichever occurred first. The secondary endpoints included overall survival (OS), objective response rate (ORR), time to response (TTR) and duration of response (DOR). Tumour assessments were performed every 8 weeks during the first 24 months and every 12 weeks thereafter until progression or end of treatment. The statistical methods employed were appropriate for the endpoints studied. To control for Type I error, a hierarchical testing procedure was applied for the PFS comparisons of Combo 450 vs vemurafenib, Combo 450 vs encorafenib, and Combo 300 vs encorafenib. The secondary endpoint of OS for Combo 450 vs vemurafenib was to be tested only if the former comparisons were statistically significant.

In Part 1, a total of 577 patients were randomised equally: 192 patients in the Combo 450 group, 194 patients in the encorafenib group and 191 patients in the vemurafenib group. The median age of patients was 56.0 years (range 20 to 89) and 26.2% were aged ≥65 years. Slightly more than half (57.9%) of the patients were males. The majority of the patients (90.3%) were Caucasian and 3.3% were Asian; 72.1% of patients had baseline ECOG performance status of 0, 95.5% patients had metastatic (Stage IV) disease and 63.8% were Stage IV M1C. Most patients had BRAF V600E mutation (88.6%) and 10.9% were V600K mutant. A total of 31.9% of patients had received prior systemic antineoplastic regimens and 29.8% had received prior immunotherapy in any disease setting (metastatic and adjuvant), including interferons/interleukins in 26.7% of patients, ipilimumab in 4.2% of patients, and anti-PD1/PDL1 in 0.5%.

In Part 2, a total of 344 patients were randomised in a 3:1 ratio: 258 patients in the Combo 300 group and 86 patients in the encorafenib group. Encorafenib patients from Part 1 (N=194) and Part 2 (N=86) were combined and analysed together in the encorafenib (Parts 1 + 2) group (N=280). In the overall population (N=538), the median age was 56.0 years (range 19 to 94), 56.3% of patients were males, 90.7% were Caucasian, and 5.2% were Asian. The majority of the patients had metastatic disease (96.5%); 17.8% had Stage IV M1B and 65.1% had Stage IV M1C. Most patients had BRAF V600E mutation (88.7%) and 11.0% had V600K mutation; 27.7% of patients had received prior immunotherapy.

Summary of key efficacy results

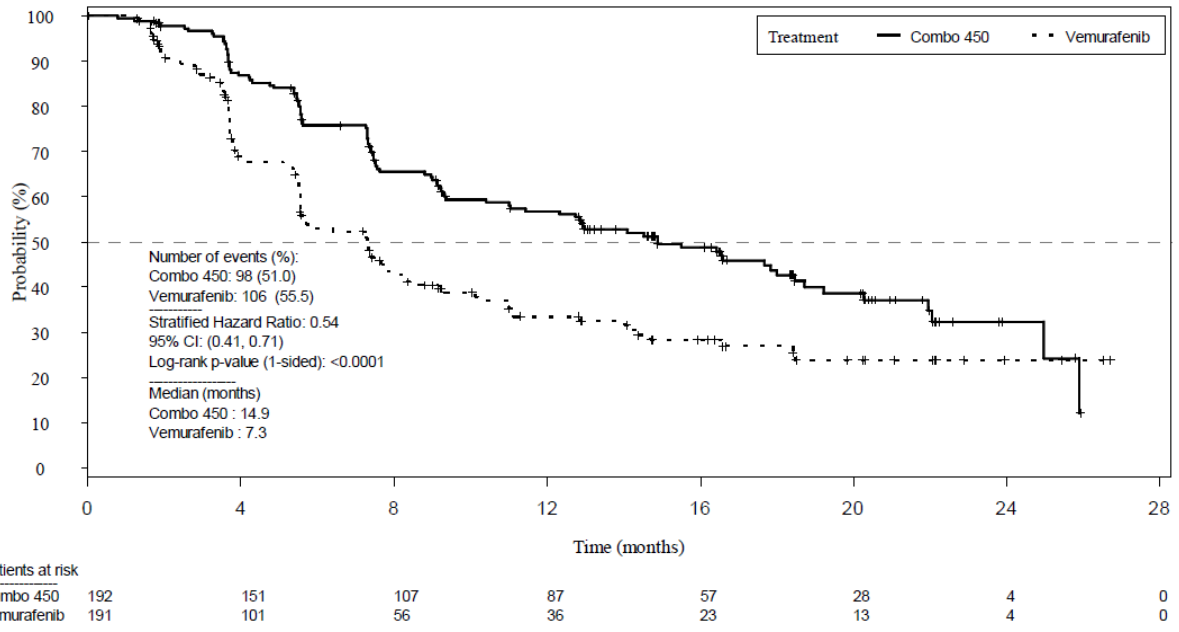
Part 1	Combo 450 (N=192)	Encorafenib (N=194)	Vemurafenib (N=191)
Primary endpoint			
PFS per BIRC			
PFS events, n (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median PFS (months) (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5, 14.8)	7.3 (5.6, 8.2)
Stratified HR (95% CI) (vs vemurafenib)[a] Stratified p-value[b]	0.54 (0.41, 0.71) <0.001		
Stratified HR (95% CI) (vs vemurafenib)[a] Nominal p-value[b]		0.68 (0.52, 0.90) 0.004[c]	
Stratified HR (95% CI) (vs encorafenib)[a] Stratified p-value[b]	0.75 (0.56, 1.00) 0.026		
Secondary endpoints			
OS			
OS events, n (%)	105 (54.7)	106 (54.6)	127 (66.5)
Median OS (months) (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Stratified HR (95% CI) (vs vemurafenib)[a] Nominal p-value[b]	0.61 (0.47, 0.79) <0.0001[c]		
Stratified HR (95% CI) (vs encorafenib)[a] Nominal p-value[b]	0.81 (0.61,1.06) 0.061[c]		
ORR per BIRC			
Confirmed ORR, % (95% CI)	63.0 (55.8, 69.9)	50.5 (43.3, 57.8)	40.3 (33.3, 47.6)
DOR			
Median (months) (95% CI)	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)

Data cut-off date for PFS, ORR and DOR was 19 May 2016; data cut-off date for OS was 07 Nov 2017.
[a] Hazard ratio based on a stratified Cox proportional hazard model, stratified by AJCC stage and ECOG performance status.
[b] One-sided p-value based on log-rank test, stratified by AJCC stage and ECOG performance status.
[c] As the comparison of PFS between Combo 450 and encorafenib was not statistically significant, as per the hierarchical testing procedure, statistical testing stopped and nominal p-values are presented for descriptive purpose only.

Part 2	Combo 300 (N=258)	Encorafenib (N=280; 194 from Part 1 and 86 from Part 2)
Primary endpoint		
PFS per BIRC		
Median PFS (months) (95% CI)	12.9 (10.1, 14.0)	9.2 (7.4 11.0)
Stratified HR (95% CI)[a] Nominal p-value[b]	0.77 (0.61, 0.97) 0.015	
Secondary endpoints		
ORR per BIRC		
Confirmed ORR, % (95% CI)	65.9 (59.8, 71.7)	50.4 (44.3, 56.4)
DOR		
Median (months) (95% CI)	12.7 (9.3, 15.1)	12.9 (8.9, 15.5)

Data cut-off date was 9 Nov 2016.
[a] Hazard ratio based on a stratified Cox proportional hazard model, stratified by AJCC stage and ECOG performance status.
[b] One-sided p-value based on log-rank test, stratified by AJCC stage and ECOG performance status.
[c] As the comparison of PFS between Combo 450 and encorafenib in Part 1 was not statistically significant, as per the hierarchical testing procedure, formal statistical testing stopped and nominal p-values are presented for descriptive purpose only.

In Part 1, the primary analysis of PFS demonstrated a statistically significant improvement for subjects in the Combo 450 group compared to the vemurafenib group (HR 0.54; 95% CI: 0.41, 0.71; p<0.001). The median duration of PFS was 14.9 months in the Combo 450 group compared to 7.3 months in the vemurafenib group, which was a 7.6-month difference. Pre-specified sensitivity analyses of PFS yielded similar results to that of the primary analysis, reflecting the robustness of the PFS benefit.



For the comparison of the Combo 450 group versus the encorafenib group, the difference in PFS was not statistically significant (median 14.9 months versus 9.6 months; HR 0.75; 95% CI: 0.56, 1.00; p=0.026).

As the analysis of PFS for Combo 450 versus encorafenib was not statistically significant, per protocol-specified testing hierarchy, the data in the OS analysis are summarised descriptively

without formal testing. The median OS was 33.6 months in the Combo 450 group and 16.9 months in the vemurafenib group (HR 0.61; 95% CI: 0.47, 0.79; nominal p<0.0001). The median OS was 33.6 months in the Combo 450 group and 23.5 months in the encorafenib group (HR 0.81; 95% CI: 0.61, 1.06; nominal p=0.061). The median DOR was numerically longer in the Combo 450 group (16.6 months) compared to the encorafenib (14.9 months) or vemurafenib group (12.3 months). The median TTR was similar in the Combo 450 group (1.9 months) compared to encorafenib (2.0 months) or vemurafenib group (2.1 months). The ORR (63.0%) and CR rates (7.8%) were numerically higher in the Combo 450 group compared to either monotherapy group (ORR range: 40% to 51%; CR range: 5.2% to 5.8%).

In Part 2, the median PFS was 12.9 months in the Combo 300 group and 9.2 months in the encorafenib group (HR 0.77; 95% CI: 0.61, 0.97; nominal p=0.015). The ORR was numerically higher in the Combo 300 group compared to the encorafenib group (65.9% versus 50.4%). However, the median DOR was similar between the Combo 300 and encorafenib groups (12.7 months versus 12.9 months).

Overall, efficacy of the combination of binimetinib and encorafenib in the treatment of unresectable or metastatic melanoma patients with a BRAF V600E or V600K mutation was adequately demonstrated in terms of clinically relevant improvements in PFS, OS, ORR and DOR compared to vemurafenib. The results of Part 1 and Part 2 of the study demonstrated the incremental benefit of adding binimetinib to encorafenib as Combo 300 performed numerically better in terms of PFS and ORR compared to encorafenib monotherapy. In addition, although the ORR were similar between Combo 450 and Combo 300, the Combo 450 group resulted in numerically longer PFS and DOR compared to Combo 300 indicating that better responses were obtained with the higher dose of encorafenib.

D ASSESSMENT OF CLINICAL SAFETY

The safety data of the combination of binimetinib + encorafenib was derived primarily from the pivotal Phase III study COLUMBUS, in which a total of 570 patients with unresectable or metastatic BRAF V600 mutant melanoma were treated: 192 patients in the Combo 450 group (binimetinib 45 mg twice daily + encorafenib 450 mg once daily), 192 patients in the encorafenib 300 mg once daily group, and 186 patients in the vemurafenib 960 mg twice daily group.

In addition, the proposed combination of binimetinib + encorafenib was evaluated in a total of 274 patients with unresectable or metastatic BRAF V600 mutant melanoma pooled across three clinical studies (Pooled Combo 450). These included 192 patients from Study COLUMBUS (Part 1), 75 patients from Study CLGX818X2109 (Group A) and 7 patients from Study CMEK162X2110. The median duration of exposure was 50.6 weeks in the pooled Combo 450 group.

In COLUMBUS Part 1, the median duration of binimetinib + encorafenib exposure was longer in the Combo 450 arm compared to the vemurafenib arm (51.2 weeks vs 26.3 weeks) and a higher proportion of patients in the Combo 450 arm were exposed to treatment for ≥48 weeks (52.6% vs 25.3%). Approximately half of the patients (49.3%) received study treatment during at least 12 months in the Combo 450 arm, versus 38.5% in the encorafenib arm and 22.6% in the vemurafenib arm.

Duration of exposure to study treatment

	Pooled	Study COLUMBUS Part 1

	Combo 450 (N=274)	Combo 450 (N=192)	Encorafenib (N=192)	Vemurafenib (N=186)
Median (weeks)	50.64	51.21	31.36	26.29
Exposure ≥48 weeks (n, %)	142 (51.8)	101 (52.6)	75 (39.1)	47 (25.3)

Overview of safety profile

AE	Pooled Combo 450 (N=274)	Study COLUMBUS Part 1		
		Combo 450 (N=192)	Encorafenib (N=192)	Vemurafenib (N=186)
Any AE	271 (98.9%)	189 (98.4%)	191 (99.5%)	186 (100.0%)
Treatment-related AE	249 (90.9%)	171 (89.1%)	191 (99.5%)	181 (97.3%)
Grade 3/4 AE	168 (61.3%)	115 (59.9%)	128 (66.7%)	118 (63.4%)
Treatment-related Grade 3/4 AE	95 (34.7%)	70 (36.5%)	96 (50.0%)	85 (45.7%)
SAE	110 (40.1%)	69 (35.9%)	67 (34.9%)	71 (38.2%)
Treatment-related SAE	31 (11.3%)	22 (11.5%)	33 (17.2%)	25 (13.4%)
AE leading to treatment discontinuation	32 (11.7%)	28 (14.6%)	29 (15.1%)	30 (16.1%)
On-treatment deaths	28 (10.2%)	19 (9.9%)	15 (7.8%)	19 (10.2%)

In COLUMBUS Part 1, the most frequently reported AEs (≥20% of patients) in the Combo 450 group were nausea (43.2%), diarrhoea (37.0%), vomiting (30.2%), fatigue (29.2%), arthralgia (26.6%), blood creatine phosphokinase (CK) increased (22.9%), headache (22.9%), constipation (22.4%), and asthenia (20.3%). In the encorafenib group, the most frequently reported AEs included alopecia (56.3%), palmar-plantar erythrodysesthesia (PPE) syndrome (51.0%), arthralgia (43.8%), hyperkeratosis (38.5%), nausea (38.5%), dry skin (30.2%), myalgia (28.6%), vomiting (28.1%), headache (27.6%), palmoplantar keratoderma (26.0%), fatigue (25.0%), pain in extremity (22.4%), pruritus (21.9%), asthenia (20.8%), decreased appetite (20.8%), and rash (20.8%). In the vemurafenib group, the most frequent AEs included arthralgia (44.6%), alopecia (36.6%), nausea (34.9%), diarrhoea (34.4%), fatigue (30.6%), rash (29.0%), hyperkeratosis (29.0%), pyrexia (28.0%), photosensitivity reaction (24.7%), keratosis pilaris (23.1%), and dry skin (22.6%).

The AEs reported at a higher incidence in the Combo 450 group than in the encorafenib group (≥10% difference) included blood CK increased (22.9% vs 1.0%), diarrhoea (37.0% vs 13.5%), and vision blurred (16.1% vs 2.1%). The AEs reported at a higher incidence in the Combo 450 group than in the vemurafenib group were vomiting (30.2% vs 15.6%), blood CK increased (22.9% vs 2.2%), constipation (22.4% vs 6.5%), abdominal pain (17.2% vs 7.0%), vision blurred (16.1% vs 2.2%), and dizziness (14.1% vs 2.7%).

The incidence of serious AEs (SAEs) was similar in the different groups: 35.9%, 34.9% and 38.2% of patients in the Combo 450, encorafenib and vemurafenib groups, respectively. The most frequently reported SAEs (≥2%) in the Combo 450 arm included nausea (1.0% in Combo 450 group, 3.1% in encorafenib group and none in vemurafenib group), pneumonia (1.6% in Combo 450 group and none in encorafenib and vemurafenib groups), and pyrexia (3.1% in Combo 450 group, 1.6% in encorafenib group and 1.1% in vemurafenib group). SAEs with a suspected relationship to study drug as assessed by the investigator were reported at a lower incidence in the Combo 450 group (11.5%) than the encorafenib (17.2%) or vemurafenib groups (13.4%).

The incidence of AEs leading to treatment discontinuation was 14.6% in the Combo 450 group, 15.1% in the encorafenib group and 16.1% in the vemurafenib group. The AEs leading to study drug discontinuation in the Combo 450 arm included increased ALT and AST (2.6% in Combo 450 group, none in encorafenib group and 1.1% in vemurafenib group).

The incidence of on-treatment deaths was 9.9% in the Combo 450 group, 7.8% in the encorafenib group and 10.2% in the vemurafenib group. The causes of death in the Combo 450 arm included malignant melanoma (6.3%), cerebral haemorrhage, completed suicide, euthanasia, metastases to central nervous system, and multiple organ dysfunction syndrome (0.5% each). However, none of the deaths were considered to be related to the study drugs by the investigator.

The most frequently reported AEs of special interest (AESI, >20%) in the Combo 450 arm were retinopathy excluding retinal vein occlusion (48.4%), rash (26.0%), liver function test (LFT) abnormalities (25.0%) and muscle enzyme/ protein changes (22.9%). The AEs of special interest have been adequately described as warnings and precautions in the proposed package insert.

Most frequently reported AESIs (>20%)

AESI	Pooled Combo 450 (N=274)	Study COLUMBUS Part 1		
		Combo 450 (N=192)	Encorafenib (N=192)	Vemurafenib (N=186)
LFT abnormalities	69 (25.2%)	48 (25.0%)	28 (14.6%)	39 (21.0%)
Rash	65 (23.7%)	50 (26.0%)	95 (49.5%)	111 (59.7)
Retinopathy excluding retinal vein occlusion	144 (52.6%)	93 (48.4%)	26 (13.5%)	23 (12.4%)
Muscle enzyme/protein changes	74 (27.0%)	44 (22.9%)	3 (1.6%)	4 (2.2%)

Overall, the safety profile of binimetinib in combination with encorafenib was considered acceptable and manageable, and was consistent with that documented for MEK and BRAF inhibitors.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current treatment options for metastatic melanoma include immune checkpoint inhibitors, kinase inhibitors and BRAF inhibitors. However, about 10–20% of cases remain fatal. Therefore, there is a need for therapies with improved survival.

Part 1 of study COLUMBUS demonstrated a clinically meaningful and statistically significantly longer median PFS in the Combo 450 group compared to the vemurafenib group (14.9 months versus 7.3 months; HR 0.54; 95% CI: 0.41, 0.71; p<0.001).

The primary endpoint results were supported by the secondary endpoints, whereby the median PFS was numerically longer in the Combo 450 group compared to the encorafenib group (14.9 months versus 9.6 months; HR 0.75; 95% CI: 0.56, 1.00; p=0.026). In addition, the median OS was numerically longer in the Combo 450 group compared to the monotherapy groups (33.6 months in the Combo 450 group versus 23.5 months in the encorafenib group and 16.9 months in the vemurafenib group). The median TTR was similar between groups at about 2 months. The ORR was numerically higher in the Combo 450 group compared to the vemurafenib and encorafenib groups (63% versus 40% to 51%). The median DOR was also numerically longer in the Combo 450 group compared to the monotherapy groups (16.6 months versus 12.3 to 14.9 months).

Part 2 of the study demonstrated a numerically longer median PFS in the Combo 300 group compared to the encorafenib group (12.9 months versus 9.2 months; HR 0.77; 95% CI: 0.61,

0.97; nominal p=0.015). With regard to the secondary endpoints, the ORR was numerically higher in the Combo 300 group compared to the encorafenib group (65.9% versus 50.4%). The median DOR was similar between the Combo 300 and encorafenib groups (12.7 months versus 12.9 months).

Overall, the results of the study demonstrated the incremental benefit of adding binimetinib to encorafenib based on the observation of improved efficacy for Combo 300 compared to encorafenib monotherapy. In addition, Combo 450 performed numerically better compared to Combo 300 supporting the use of the higher dose of encorafenib.

The combination treatment was associated with more AEs than monotherapy, however, this was not unexpected due to the presence of more drugs. The most common AEs with Combo 450 were nausea, diarrhoea, vomiting, fatigue, arthralgia, blood CK increased, constipation, headache and asthenia. The incidences of SAEs, discontinuation due to AEs and deaths were comparable between the Combo 450 and monotherapy groups. In addition, none of the deaths were considered to be related to the study drugs by the investigators.

Taken together, the benefit-risk profile of binimetinib in combination with encorafenib for the treatment of adult patients who have unresectable or metastatic melanoma with a BRAF V600E or V600K mutation was considered to be favourable as efficacy was demonstrated and the safety profile was manageable and consistent with what is known for the MEK and BRAF inhibitor classes of drugs.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of binimetinib in combination with encorafenib for the treatment of adult patients who have unresectable or metastatic melanoma with a BRAF V600E or V600K mutation was deemed favourable and approval of the product registration was granted on 19 July 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

▼ This therapeutic product is subject to additional monitoring in Singapore. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at HSA: Healthcare professionals' guide to adverse events reporting.

PRODUCT INFORMATION

1. NAME OF THE MEDICINE

MEKTOVI®
binimetinib
film-coated tablets

Binimetinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MEKTOVI film-coated tablet contains binimetinib 15mg. Contains lactose. Contains sugars. For a full list of excipients, see section 6.1 *List of excipients*.

3. PHARMACEUTICAL FORM

MEKTOVI 15 mg film-coated tablets are yellow/dark yellow, unscored biconvex, ovaloid film-coated tablets, approximately 12 mm in length and 5 mm in width, with the "A" logo debossed on one face of the tablet and "15" on the opposing face.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by a validated test.

4.2. DOSE AND METHOD OF ADMINISTRATION

Treatment with binimetinib in combination with encorafenib should only be initiated and supervised by a physician experienced in the use of anti-cancer medicines.

Dosage
Patients treated with binimetinib in combination with encorafenib must have their BRAF V600 mutant melanoma status confirmed by a validated test conducted by an experienced laboratory (see 5.1 Clinical Trials).
The recommended dose of binimetinib is 45 mg (three 15 mg tablets) twice daily (corresponding to a total dose of 90 mg), approximately 12 hours apart, when used in combination with encorafenib.

Administration
Binimetinib tablets should be swallowed whole with water, with or without food.

Duration of treatment
Treatment should continue until the patient no longer derives benefit or unacceptable toxicity develops.

Missed dose
If a dose of binimetinib is missed, it should not be taken if it is less than 6 hours until the next dose is due.

Vomiting after administration
If a patient vomits after administration of binimetinib, the patient should not take the dose again. The patient should take the next scheduled dose.

Dose modification
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation (see below and Table 1). The decision on whether to modify the dose of binimetinib should be based on the prescriber's assessment of individual patient safety and tolerance.

The recommended reduced dose of binimetinib is 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily.

If the adverse reaction that resulted in a dose reduction is under effective management, re-escalation to 45 mg twice daily may be considered. Dose-re-escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventricular dysfunction (LVD) or any Grade 4 toxicity.

If treatment-related toxicities occur when binimetinib is used in combination with encorafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for encorafenib only (adverse reactions primarily related to encorafenib) are: palmar-plantar erythrodysaesthesia syndrome (PPES), uveitis including iritis and iridocyclitis, and QTc prolongation.

If one of these toxicities occurs, see section 4.2. *Dose and Method of Administration* of encorafenib PI for dose modification instructions for encorafenib.

If binimetinib is temporarily interrupted, reduce encorafenib to 300 mg once daily during the time of binimetinib dose interruption (see Table 1) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib may be continued (at the reduced dose of 300 mg) depending on the individual clinical benefit.

If encorafenib is temporarily interrupted (see section 4.2 *Dose and Method of Administration* of encorafenib PI), interrupt binimetinib. If encorafenib is permanently discontinued, then discontinue binimetinib.

Dose modification recommendations in case of adverse reactions are presented in Table 1. For information on the dosage and recommended dose modifications of encorafenib, refer to the encorafenib PI, section 4.2 *Dose and Method of Administration*.

Table 1: Recommended dose modification for adverse reactions with binimetinib (used in combination with encorafenib) for selected adverse reactions

Table 1: Recommended dose modification for adverse reactions with binimetinib (used in combination with encorafenib) for selected adverse reactions

Severity of adverse reaction[a]	Recommended binimetinib dose modification
Cutaneous reactions	
Grade 2	Maintain binimetinib If rash worsens or does not improve within 2 weeks with treatment, withhold binimetinib until Grade 0 or 1 and then resume at the same dose if first occurrence or resume at a reduced dose if recurrent Grade 2.
Grade 3	Withhold binimetinib until improved to Grade 0 or 1 and resume at the same dose if first occurrence or resume at a reduced dose if recurrent Grade 3.
Grade 4	Permanently discontinue binimetinib.
Ocular events	
Symptomatic retinal pigment epithelial detachment (RPED) (Grade 2 or 3)	Withhold binimetinib for up to 2 weeks and repeat ophthalmic monitoring including visual acuity assessment. • If improved to Grade 0 or 1, resume binimetinib at same dose • If improved to Grade 2, binimetinib should be resumed at a lower dose. • If not improved to Grade 2, binimetinib should be permanently discontinued.
Symptomatic RPED (Grade 4) associated with reduced visual acuity	Permanently discontinue binimetinib.
Retinal vein occlusion (RVO)	Permanently discontinue binimetinib.
Cardiac events	
Grade 2 left ventricular ejection fraction (LVEF) decrease or asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is below lower limit of normal (LLN)	Evaluate LVEF every 2 weeks. • If asymptomatic: Withhold binimetinib for up to 4 weeks. Resume binimetinib at a reduced dose if all of the following are present within 4 weeks: - LVEF at or above the LLN and - Absolute decrease from baseline is 10% or less. • If the LVEF does not recover within 4 weeks, permanently discontinue binimetinib.
Grade 3 or 4 LVEF decrease or symptomatic LVD	Permanently discontinue binimetinib. Evaluate LVEF every 2 weeks until recovery.
Rhabdomyolysis/Creatine phosphokinase (CK) elevation	
Grade 3 (CK > 5 – 10 x upper limit of normal (ULN) asymptomatic	Maintain binimetinib dose and ensure patient is adequately hydrated.
Grade 4 (CK > 10 x ULN) asymptomatic	Withhold binimetinib until improved to Grade 0 or 1. Ensure patient has adequate hydration.
Grade 3 or 4 (CK > 5 x ULN) with muscle symptoms or renal impairment	Withhold binimetinib until improved to Grade 0 or 1 • If resolved within 4 weeks, resume binimetinib at a reduced dose, or • Permanently discontinue binimetinib.
Venous thromboembolism	
Uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) ≤ Grade 3	Withhold binimetinib • If improved to Grade 0 or 1, resume at a reduced dose. • If not improved, permanently discontinue binimetinib.
Grade 4 PE	Permanently discontinue binimetinib.
Liver laboratory abnormalities	
Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x – ≤ 5 x upper limit of normal (ULN)	Maintain binimetinib dose If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0 or 1 or to baseline levels, and then resume at the same dose.
First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, resume binimetinib at reduced dose, or • If not improved, permanently discontinue binimetinib.
First occurrence of Grade 4 (AST or ALT > 20 ULN)	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, resume binimetinib at a reduced dose level, or • If not improved, permanently discontinue binimetinib. Or, binimetinib should be permanently discontinued.
Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Consider permanently discontinuing binimetinib.
Recurrent Grade 4 (AST or ALT > 20 ULN)	Permanently discontinue binimetinib.
Interstitial lung disease (ILD)/pneumonitis	
Grade 2	Withhold binimetinib for up to 4 weeks • If improved to Grade 0 or 1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.
Grade 3 or 4	Permanently discontinue binimetinib.
Other	
Recurrent or intolerable Grade 2 adverse reactions First occurrence of Grade 3 adverse reactions	Withhold binimetinib for up to 4 weeks • If improved to Grade 0 or 1 or baseline level, resume at a reduced dose. • If not improved, permanently discontinue binimetinib.
First occurrence of Grade 4 adverse reactions	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, then resume at a reduced dose. • If not improved, permanently discontinue binimetinib. Or, permanently discontinue binimetinib.
Recurrent Grade 3 adverse reactions	Consider permanently discontinuing binimetinib.
Recurrent Grade 4 adverse reactions	Permanently discontinue binimetinib.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A). As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimetinib is not recommended in these patients (see section 4.2 *Dose and method of administration* of encorafenib PI).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2 *Pharmacokinetic properties*).

Elderly patients (65 years and older)
No dose adjustment is required for elderly patients (see section 5.2 *Pharmacokinetic properties*).

Children and adolescents (< 18 years)
The safety and efficacy of binimetinib have not been established in patients below the age of 18 years. There are no data available.

4.3. CONTRAINDICATIONS

Hypersensitivity to the active substance binimetinib or to any of the excipients (see section 6.1 *List of excipients*).

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

When binimetinib is given in combination with encorafenib, the PI for encorafenib must be consulted prior to initiation of combination treatment. For additional information on warnings and precautions associated with encorafenib treatment, please refer to the PI for encorafenib.

BRAF mutation testing
Before taking binimetinib in combination with encorafenib, patients must have their BRAF V600 mutant melanoma status confirmed by a validated test to minimise false-positive and false-negative determinations. The efficacy and safety of binimetinib in combination with encorafenib were only established in patients with tumours expressing BRAF V600E and V600K mutations. Binimetinib in combination with encorafenib should not be used in patients with wild-type BRAF malignant melanoma.

Binimetinib in combination with encorafenib in patients who have progressed on a BRAF inhibitor
There are limited data on the use of the combination of binimetinib with encorafenib in patients who previously progressed on a prior BRAF inhibitor treatment for unresectable or metastatic melanoma with a BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients.

Binimetinib in combination with encorafenib in patients with brain metastases
There are limited efficacy data on the use of the combination of binimetinib and encorafenib in patients with a BRAF V600 mutant melanoma with brain metastases (see section 5.1 *Pharmacodynamic properties*).

Left ventricular dysfunction
Left ventricular dysfunction, defined as symptomatic or asymptomatic decreases in ejection fraction can occur with the use of binimetinib.

It is recommended that LVEF is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of binimetinib, 1 month after initiation and then at approximately 3-month intervals or more frequently as clinically indicated while on treatment. The occurrence of LVEF decrease can be managed with dose reduction, treatment interruption or treatment discontinuation (see section 4.2 *Dose and method of administration*).

The safety of binimetinib in combination with encorafenib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional LLN. Therefore, in these patients, binimetinib should be used with caution and for any symptomatic LVD, Grade 3 or 4 LVEF, or absolute decrease of LVEF from baseline of ≥ 10 %, binimetinib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Venous thromboembolism
Venous thromboembolism (VTE) can occur with the use of binimetinib. (see section 4.8 *Adverse effects (undesirable effects)*). Binimetinib should be used with caution in patients who are at risk of, or with a history of VTE.

If during treatment the patient develops VTE or pulmonary embolism, it should be managed with dose reduction, treatment interruption or treatment discontinuation (see section 4.2 *Dose and method of administration*).

Haemorrhage
Haemorrhages, including major haemorrhagic events, can occur when binimetinib is administered with encorafenib (see section 4.8 *Adverse effects (undesirable effects)*). The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ≥ 3 haemorrhagic events should be managed with dose reduction, treatment or treatment discontinuation; as clinically indicated (see section 4.2 *Dose and method of administration*).

Ocular toxicities
Ocular toxicities including RPED and RVO can occur when binimetinib is administered. Uveitis, including iridocyclitis and iritis, was reported in patients treated with binimetinib in combination with encorafenib see section 4.8 *Adverse effects (undesirable effects)*).

Binimetinib is not recommended in patients with a history of RVO. The safety of binimetinib has not been established in patients with predisposing factors for RVO including uncontrolled glaucoma, ocular hypertension, uncontrolled diabetes mellitus or a history of hyperviscosity or hypercoagulability syndromes. Binimetinib should therefore be used with caution in these patients.

Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended.

The occurrence of symptomatic RPED can be managed with dose reduction, treatment interruption or treatment discontinuation (see Table 1 in section 4.2 *Dose and method of administration*). Binimetinib should be permanently discontinued with the occurrence of RVO (see Table 1 in section 4.2 *Dose and method of administration*).

If a patient develops uveitis during treatment, see section 4.2 of encorafenib PI for guidance.

CK elevation and rhabdomyolysis
Asymptomatic CK elevations are seen in patients treated with binimetinib in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)*). Across clinical trials of binimetinib in combination with encorafenib, rhabdomyolysis was uncommonly reported. Special attention should be paid to the use of binimetinib in patients with neuromuscular conditions associated with CK elevation and rhabdomyolysis.

CK and creatinine levels should be monitored monthly during the first 6 months of treatment and as clinically indicated. The patient should be advised to maintain an adequate fluid intake during treatment. Depending on the severity of symptoms, degree of CK elevation or creatinine elevation, dose reduction, dose interruption or permanent discontinuation of binimetinib may be required (see section 4.2 *Dose and Method of Administration*).

New primary malignancies
New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when binimetinib is administered in combination with encorafenib.

Cutaneous malignancies
Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma has been observed in patients treated with binimetinib when used in combination with encorafenib.
Dermatologic evaluations should be performed prior to initiation of therapy with binimetinib in combination with encorafenib every 2 months while on therapy and for up to 6 months following discontinuation of the combination. Suspicious skin lesions should be managed with dermatological excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Encorafenib and binimetinib should be continued without any dose modifications.

Non-cutaneous malignancies
Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving binimetinib in combination with encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate. Permanent discontinuation of binimetinib and encorafenib should be considered in patients who develop RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering binimetinib in combination with encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Hypertension
Hypertension, or worsening of pre-existing hypertension, can occur with the use of binimetinib. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate. In case of severe hypertension, temporary interruption of binimetinib is recommended until hypertension is controlled (see Table 1 in section 4.2 *Dose and method of administration*).

Pneumonitis/Interstitial lung disease (ILD)
Pneumonitis/interstitial lung disease (ILD) can occur with binimetinib. Treatment with binimetinib should be withheld in patients with suspected pneumonitis or ILD, including patients presenting new or progressive pulmonary symptoms or findings such as cough, dyspnoea, hypoxia, reticular opacities or pulmonary infiltrates (see Table 1 in section 4.2 *Dose and method of administration*). Binimetinib should be permanently discontinued in patients diagnosed with treatment related pneumonitis or ILD.

Use in hepatic impairment
Liver metabolism mainly via glucuronidation is the primary route of elimination of binimetinib (see section 5.2 *Pharmacokinetic properties*). As encorafenib is not recommended in patients with moderate (Child Pugh B) and severe hepatic impairment (Child Pugh C), administration of binimetinib is not recommended in these patients (see sections 4.2 *Dose and method of administration* and 5.2 *Pharmacokinetic properties*).

Lactose intolerance
MEKTOVI contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MEKTOVI.

Use in the elderly
Please refer to sections 5.2 *Pharmacokinetic properties* and 4.8 *Adverse effects (undesirable effects)*.

Paediatric use
The safety and efficacy of binimetinib in children and adolescents aged < 18 years have not yet been established. There are no data available.

Effects on laboratory tests
Liver laboratory abnormalities (AST, ALT elevations) can occur with binimetinib (see section 4.8 *Adverse effects (undesirable effects)*). Liver laboratory values should be monitored before initiation of binimetinib and encorafenib and at least monthly during the first 6 months of treatment and then as clinically indicated. Liver function abnormalities should be managed with dose reduction, treatment interruption or treatment discontinuation (see section 4.2 *Dose and method of administration*).

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of UGT1A1 and UGT2B7 inducers or inhibitors on binimetinib
Binimetinib is primarily metabolised by UGT1A1 and UGT2B7 mediated glucuronidation and to a lesser extent by CYP1A2-and CYP2C19-mediated oxidation. In a clinical study sub- analysis however, there was no apparent relationship observed between binimetinib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGT1A1 inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib C_{max} in the presence or absence of atazanavir. Since binimetinib is metabolised by multiple enzymes, the possible extent of drug interactions mediated by UGT1A1, UGT2B7, CYP1A2 or CYP2C19 is minimal and unlikely to be clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 or UGT2B7 inducers (such as rifampicin and phenobarbital), UGT1A1 inhibitors (such as indinavir, atazanavir and sorafenib) and UGT2B7 inhibitors (quinidine, mefenamic acid and diclofenac) should be co-administered with caution.

Combination with encorafenib
While encorafenib is a relatively potent reversible inhibitor of UGT1A1, no differences in binimetinib exposure have been observed clinically when binimetinib is co-administered with encorafenib.

Effect of transporters on binimetinib
In vitro experiments indicate that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein. Co-administration of binimetinib with inhibitors of these transporters may increase the plasma binimetinib concentration in patients.

No clinically relevant drug interactions have been demonstrated with binimetinib.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effect of binimetinib on fertility in humans.

Fertility studies were not conducted with binimetinib. In repeat-dose toxicity studies, no concern on reproductive organs were observed in rats or monkeys (animal: human exposure ratios up to 19 and 0.4, respectively). It is uncertain whether binimetinib may affect fertility in patients.

Women of childbearing potential
Women of childbearing potential should be advised to use effective contraception during treatment with binimetinib and for at least 1 month after the last dose. Women of childbearing potential receiving binimetinib in combination with encorafenib should be advised that encorafenib may decrease efficacy of hormonal contraceptives. Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment with encorafenib and for at least 1 month following the last dose.

Use in pregnancy
Category D.

There are no data on the use of binimetinib in pregnant women. However, studies in animals have demonstrated reproductive toxicity. The potential embryo-foetal effects of binimetinib were evaluated in rats and rabbits. In rats, lower gestational body weight gain and foetal body weight were noted at ≥ 30 mg/kg/d and a decreased number of ossified foetal sternebrae was noted at ≥ 10 mg/kg/d (8 times the clinical exposure). The NOAEL in rats was 10 mg/kg/d. In rabbits, mortality, maternal physical signs of toxicity, lower gestational body weight and abortion were noted at ≥ 10 mg/kg/d (1.4 times the clinical exposure). From 10 mg/kg/d, the number of viable foetuses and foetal body weights were reduced and post- implantation loss and resorptions were increased. At 20 mg/kg/d, increased litter incidences of foetal ventricular septal defects, dilated aortic arch and pulmonary trunk alterations were noted. The NOAEL in rabbit was 2 mg/kg/d (0.5 times the clinical exposure).

If administered to pregnant women, binimetinib may harm the foetus. Binimetinib should not be administered during pregnancy unless the benefits for the mother clearly outweigh the risks for the foetus.

Use in lactation
It is not known if binimetinib or its active metabolite is excreted in human milk. Because many drugs are excreted in breast milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue binimetinib or to discontinue nursing, taking into account the benefit of breast feeding for the child and the benefit of the drug to the mother.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Visual disturbances have been reported in patients treated with binimetinib during clinical trials. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse effects that may affect their ability to drive or use machines (see section 4.8 *Adverse effects (undesirable effects)*).

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile
The safety of binimetinib (45 mg orally twice daily) in combination with encorafenib (450mg orally once daily) (hereafter referred to as the pooled Combo 450 population) was evaluated in 274 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, based on two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301).

At the recommended Combo 450 dose in patients with metastatic melanoma (n=274), the most common adverse reactions (≥ 25%) occurring in patients treated with binimetinib in combination with encorafenib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, arthralgia, blood CK increased and myalgia.

The safety of encorafenib (300 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 257 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the Combo 300 population), based on the Phase III study (CMEK162B2301, Part 2). The most common adverse reactions (≥ 25%) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea.

Tabulated summary of adverse reactions
Adverse reactions in the pooled Combo 450 population (n=274) are listed in Table 2 by MedDRA body system organ class (SOC).

Table 2: Adverse reactions occurring in patients receiving binimetinib in combination with encorafenib at the recommended dose (n = 274)

Table 2: Adverse reactions occurring in patients receiving binimetinib in combination with encorafenib at the recommended dose (n = 274)

System Organ Class	Adverse reaction	Frequency All grades n (%)	Frequency Grades 3/4 n (%)
Neoplasms benign, malignant and unspecified	CuSCC[a]	9 (3.3)	1 (0.4)
	Basal cell carcinoma*	3 (1.1)	0
	Skin papilloma*	22 (8.03)	0
Blood and lymphatic system disorders	Anaemia	54 (19.7)	13 (4.7)
Immune system disorders	Hypersensitivity[b]	9 (3.3)	0
Nervous system disorders	Neuropathy peripheral*	36 (13.1)	3 (1.1)
	Dizziness*	42 (15.3)	7 (2.6)
	Headache*	59 (21.5)	4 (1.5)
	Dysgeusia	18 (6.6)	0
	Facial paresis[c]	2 (0.7)	1 (0.4)
Eye disorders	Visual impairment*	59 (21.5)	1 (0.4)
	RPED*	81 (29.6)	5 (1.8)
	Uveitis*	12 (4.4)	1 (0.4)
Cardiac disorders	Left ventricular dysfunction[d]	23 (8.4)	3 (1.1)
Vascular disorders	Haemorrhage[e]	49 (17.9)	9 (3.3)
	Hypertension*	32 (11.7)	15 (5.5)
	Venous thromboembolism[f]	13 (4.7)	3 (1.1)
Gastrointestinal disorders	Abdominal pain*	75 (27.4)	7 (2.6)
	Diarrhoea*	104 (38.0)	9 (3.3)
	Vomiting*	77 (28.1)	6 (2.2)
	Nausea	114 (41.6)	7 (2.6)
	Constipation	66 (24.1)	0
	Colitis[g]	6 (2.2)	2 (0.7)
	Pancreatitis*	2 (0.7)	2 (0.7)
Skin and subcutaneous tissue disorders	Hyperkeratosis *	57 (20.8)	1 (0.4)
	Rash *	54 (19.7)	2 (0.7)
	Dry skin*	40 (14.6)	0
	Pruritus*	32 (11.7)	1 (0.4)
	Alopecia*	40 (14.6)	0
	Photosensitivity*	11 (4.0)	1 (0.4)
	Dermatitis acneiform*	12 (4.4)	0
	PPES	17 (6.2)	0
	Erythema*	22 (8.0)	0
	Panniculitis*	4 (1.5)	0
Musculoskeletal and connective tissue disorders	Arthralgia*	74 (27.0)	2 (0.7)
	Muscular disorders/ Myalgia[h]	71 (25.9)	2 (0.7)
	Back pain	30 (10.9)	2 (0.7)
	Pain in extremity	29 (10.6)	4 (1.5)
	Rhabdomyolysis	1 (0.4)	1 (0.4)
Renal and urinary disorders	Renal failure*	9 (3.3)	6 (2.2)
General disorders and administration site conditions	Pyrexia*	47 (17.2)	8 (2.9)
	Peripheral oedema[i]	42 (15.3)	3 (1.1)
	Fatigue*	120 (43.8)	8 (2.9)
Investigations	Blood creatine phosphokinase increased	74 (27.0)	16 (5.8)
	Transaminase increased*	43 (15.7)	15 (5.5)
	Gamma-glutamyl transferase increased*	40 (14.6)	23 (8.4)
	Blood creatinine increased*	17 (6.2)	2 (0.7)
	Blood alkaline phosphatase increased*	20 (7.3)	2 (0.7)
	Amylase increased	9 (3.3)	4 (1.5)
	Lipase increased	14 (5.1)	7 (2.6)

* composite terms which included more than one preferred term
[a] includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma and squamous cell carcinoma of skin
[b] includes angioedema, drug hypersensitivity, hypersensitivity and hypersensitivity vasculitis and urticaria
[c] includes facial nerve disorder, facial paralysis, facial paresis
[d] includes left ventricular dysfunction, ejection decreased fraction, cardiac failure and abnormal ejection fraction
[e] includes haemorrhage at various sites including cerebral haemorrhage
[f] includes pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial and thrombosis
[g] includes colitis, colitis ulcerative, enterocolitis and proctitis
[h] includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, myositis
[i] includes fluid retention, peripheral oedema, localised oedema.

Description of selected adverse reactions

Cutaneous squamous cell carcinoma
Cutaneous squamous cell carcinoma was reported when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Ocular events
In the pooled Combo 450 population, RPED was reported in 29.6% (81/274) of patients. RPED was Grade 1 (asymptomatic) in 21.2% (58/274) of patients, Grade 2 in 6.6% (18/274) and Grade 3 in 1.8% (5/274). Most of these events were reported as retinopathy (9.5%, 26/274), retinal detachment (6.6%, 18/274), subretinal fluid (6.2%, 17/274), macular oedema (5.1%, 14/274) and chorioretinopathy (3.3%, 9/274), and led to dose interruptions or dose modifications in 4.7% (13/274) of patients. The median time to onset of the first event of RPED (all grades) was 1.5 month (range 0.03 to 17.5 months). RPED was generally reversible. Visual impairment, including vision blurred and reduced visual acuity, occurred in 21.5% (59/274) of patients. Visual impairment was generally reversible.
Uveitis was reported when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Left ventricular dysfunction
In the pooled Combo 450 population, LVD was reported in 8.4% (23/274) of patients. Grade 3 events occurred in 1.1% (3/274) of patients. LVD led to treatment discontinuation in 0.4% (1/274) of patients and led to dose interruptions or dose reductions in 6.6% (18/274) of patients.
The median time to first occurrence of LVD (any grade) was 4.4 months (range 0.03 to 21.3 months) in patients who developed an LVEF below 50%. The mean LVEF value dropped by 5.9% in the pooled Combo 450 population from a mean of 63.9% at baseline to 58.1%. LVD was generally reversible following dose reduction or dose interruption.

Haemorrhage
Haemorrhagic events have been observed in 17.9% (49/274) of patients in the pooled Combo 450 population. Most of these cases were Grade 1 or 2 (14.6%) and 3.3% were Grade 3 or 4 events. Few patients required dose interruptions or dose reductions (0.7% or 2/274).
Haemorrhagic events led to discontinuation of treatment in 1.1% (3/274) of patients. The most frequent haemorrhagic events were haematuria in 3.3% (9/274) of patients, rectal haemorrhage in 2.9% (8/274) and haematochezia in 2.9% (8/274) of patients. Fatal gastric ulcer haemorrhage with multiple organ failure as a concurrent cause of death, occurred in one patient. Cerebral haemorrhage occurred in 1.5% (4/274) of patients with fatal outcome in 3 patients. All events occurred in the setting of new or progressive brain metastases for all patients.
In Study CMEK162B2301-Part 2, in the Combo 300 arm, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3-4 in 1.6% (4/257) of patients.

Hypertension
New onset elevated blood pressure or worsening of pre-existing hypertension were reported in 11.7% (32/274) of patients treated with the Combo 450 mg. Hypertension related adverse events were reported as Grade 3 in 5.5% (15/274) of patients including hypertensive crisis (0.4% (1/274). Hypertension led to dose interruption or adjustment in 2.9% of patients.
Hypertensive adverse reactions required additional therapy in 8.0% (22/274) of patients.

Venous thromboembolism
In the pooled Combo 450 population, VTE occurred in 4.7% (13/274) of patients, including 2.2% (6/274) of patients who developed PE. VTE was reported as Grade 1 or 2 in 3.6% (10/274) of patients and Grade 3 or 4 in 1.1% (3/274) of patients. VTE led to dose interruptions or dose modifications in 1.1% (3/274) patients and to additional therapy in 4.7% (13/274) of patients.

Pancreatitis
Pancreatitis was reported when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Dermatological reactions
Rash
In the pooled Combo 450 mg population, rash occurred in 19.7% (54/274) of patients. Most of the events were mild, with Grade 3 or 4 events reported in 0.7% (2/274) of patients. Rash led to discontinuation in 0.4% (1/274) patients and to dose interruption or dose modification in 1.1% (3/274) of patients.

Palmar-plantar erythrodysaesthesia syndrome
Palmar-plantar erythrodysaesthesia syndrome (PPES) was reported when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Acneiform dermatitis
In the pooled Combo 450 population, acneiform dermatitis occurred in 4.4% (12/274) of patients with no grade 3/4 events and no event led to treatment discontinuation. Dose modification was reported in 0.7% (2/274) of patients.

Photosensitivity
In the pooled Combo 450 population, photosensitivity was observed in 4.0 % (11/274) of patients. Most events were Grade 1-2, with Grade 3 reported in 0.4 % (1/274) of patients and no event led to discontinuation. Dose interruption or dose modification was reported in 0.4 % (1/274) of patients.

Facial paresis
Facial paresis was reported when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

CK elevation/Rhabdomyolysis
In the pooled Combo 450 population, mostly mild asymptomatic blood CK elevation was reported in 27.0% (748/274) of patients. The incidence of Grade 3 or 4 adverse events was 5.8% (16/274). The median time to onset of the first event was 2.7 months (range 0.5 to 17.5 months).
Rhabdomyolysis was reported in 0.4% (1/274) of patients treated with encorafenib in combination with binimetinib. In this patient, rhabdomyolysis was observed with concomitant symptomatic Grade 4 CK elevation.

Renal dysfunction
Blood creatinine elevation and renal failure occurred when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Liver laboratory abnormalities
The incidence of liver laboratory abnormalities reported in the pooled Combo 450 population is listed below:
- ALT: 13.1 % (36/274) overall - Grade 3-4: 4.7 % (13/274)
- AST: 9.5 % (26/274) overall - Grade 3-4: 2.2 % (6/274)
- GGT: 14.6 % (40/274) overall - Grade 3-4: 8.4 % (23/274)
- Bilirubin: 0.7 %(2/274) overall - the maximum severity of these events was Grade 2

Gastrointestinal disorders
In the pooled Combo 450 population, diarrhoea was observed in 38 % (104/274) of patients and was Grade 3 or 4 in 3.3 % (9/274) of patients. Diarrhoea led to dose discontinuation in 0.4% of patients and to dose interruption or dose modification

XXXXX

XXXXX

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. You can report side efects to your doctor, or physicians.

MEKTOVI®
binimetinib
film-coated tablets

Active ingredient(s): *binimetinib*

This leaflet provides important information about using MEKTOVI. **You should also speak to your doctor or pharmacist if you would like further information or if you have any concerns or questions about using MEKTOVI.**

Where to find information in this leaflet:

1. Why am I using MEKTOVI?

MEKTOVI contains the active ingredient binimetinib
MEKTOVI is an anti-cancer medicine, which belongs to a group of medicines called 'MEK inhibitors'.

MEKTOVI is used in combination with another medicine which contains the active ingredient, encorafenib (called BRAFTOVI®) to treat adult patients with a type of skin cancer called melanoma, which has spread to other parts of the body, or cannot be removed by surgery.

The type of melanoma which MEKTOVI and BRAFTOVI are used to treat, has a particular change (mutation) in a gene called BRAF. This mutation in the BRAF gene may have produced proteins which caused the melanoma to develop.

Before you start treatment, your doctor will have tested you to confirm that you have this BRAF mutation.

MEKTOVI targets a protein called MEK which promotes cancer cell growth. When MEKTOVI is used in combination with BRAFTOVI (which targets the changed BRAF protein), it further slows down or stops the growth of your cancer.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.

Your doctor may have prescribed it for another reason. BRAFTOVI is not recommended for children and adolescents aged under 18 years. The safety and efficacy of this medicine has not been established in this age group.

2. What should I know before I use MEKTOVI?

MEKTOVI is to be used in combination with BRAFTOVI, therefore you should also read the CMI for the other medicine you are planning to take.

Warnings

Do not use MEKTOVI if:
- You are allergic to binimetinib, or any of the ingredients listed at the end of this leaflet. Some of the symptoms of an allergic reaction may include:
  - shortness of breath
  - wheezing or difficulty breathing
  - swelling of the face, lips, tongue or other parts of the body
  - rash, itching or hives on the skin
- Always check the ingredients to make sure you can use this medicine.

Check with your doctor if you:
- Have any other medical conditions such as:
  - heart problems
  - high blood pressure
  - muscle problems
  - blood clots
  - liver problems
  - lung or breathing problems
  - bleeding problems or if you are taking medicines that may increase your risk of bleeding
  - eye problems including glaucoma or increased pressure in your eyes
- Take any medicines for any other condition

MEKTOVI contains lactose. Tell your doctor, nurse or pharmacist if you have an intolerance to some sugars.

Tell your doctor if you have had a history of blockage in the vein draining the eye (retinal vein occlusion) as MEKTOVI is not recommended in patients with a history of retinal vein occlusion.

Tell your doctor if you have had a different type of cancer than melanoma as MEKTOVI when taken with BRAFTOVI may cause progression of certain other types of cancers.

During treatment, you may be at risk of developing certain side effects. It is important you understand these risks and how to monitor for them. See additional information under Section 6. *Are there any side effects*?

Pregnancy and breastfeeding
Check with your doctor if you are pregnant or intend to become pregnant.

Taking MEKTOVI during pregnancy is not recommended. Tell your doctor if you are pregnant or plan to become pregnant or are breast-feeding before taking MEKTOVI.

MEKTOVI may cause permanent harm or birth defects to an unborn baby.

Talk to your doctor if you are breastfeeding or intend to breastfeed.

MEKTOVI is not recommended while breast-feeding. If you are breastfeeding or planning to breastfeed, you must tell your doctor before taking this medicine.

It is not known if MEKTOVI passes into breastmilk.

3. What if I am taking other medicines?

Tell your doctor or pharmacist if you are taking any other medicines, including any medicines, vitamins or supplements that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with MEKTOVI and affect how it works.

Keep a list of the medicines you take so you can show it to your doctor, nurse or pharmacist when you get a new medicine.

Check with your doctor or pharmacist if you are not sure about what medicines, vitamins or supplements you are taking and if these affect MEKTOVI.

4. How do I take MEKTOVI?

How much to take
- Always take MEKTOVI exactly as your doctor has prescribed.
- The recommended dose of MEKTOVI, when taken in combination with BRAFTOVI, is three 15 mg tablets twice daily taken about 12 hours apart (corresponding to a daily dose of 90 mg).
- If you experience serious side effects (such as skin, eye, heart or lung problems), your doctor may lower the dose of MEKTOVI, or stop treatment temporarily or permanently.
- Follow the instructions provided and use MEKTOVI until your doctor tells you to stop.

When to take MEKTOVI
- Swallow the tablets whole with a full glass of water.
- MEKTOVI can be taken with or without food.
- If vomiting occurs at any time after taking the tablets do not take an additional dose. Take the next dose as scheduled.

Continue taking MEKTOVI for as long as your doctor tells you to. Do not stop unless your doctor advises you to.

If you forget to use MEKTOVI
If you miss a dose of MEKTOVI at the usual time, the missed dose is less than 6 hours late, take it as soon as you remember.

If the missed dose is more than 6 hours late, skip that dose and take your next dose at the usual time.
Then go back to taking your tablets as you would normally

Do not take a double dose to make up for the dose that you missed.

If you are not sure what to do, ask your doctor or pharmacist.

If you have trouble remembering to take your medicine, ask your doctor, nurse or pharmacist for some hints.

If you use too much MEKTOVI
If you think that you have used too much MEKTOVI, you may need urgent medical attention.

You should immediately:
- contact your doctor, or
- go to the Emergency Department at your nearest hospital.

You should do this even if there are no signs of discomfort or poisoning.

5. What should I know while using MEKTOVI?

Things you should do

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking MEKTOVI.

If you are going to have surgery, tell the surgeon or that you are taking MEKTOVI.

If you become pregnant while taking MEKTOVI, tell your doctor immediately.

If you are a woman who could become pregnant, you must use effective birth control (contraception) while you are taking MEKTOVI, and you must continue to use effective contraception for at least 1 month after taking your last dose.

Tell your doctor if you are breastfeeding while being treated with MEKTOVI.

Call your doctor straight away if you experience the following while you are taking MEKTOVI:

- **Skin changes**
MEKTOVI when taken with BRAFTOVI may cause other types of skin cancer such as cutaneous squamous cell carcinoma. Your doctor will periodically check for new cancers on your skin and inside your body before, during and after your treatment. Tell your doctor immediately if you detect any skin changes including new warts, skin soreness, reddish bumps which bleed or don't heal or any changes in the size or colour of a mole.
- **Heart problems**
MEKTOVI can lower the amount of blood pumped by your heart or make existing heart problems worse. Your doctor will run tests to check that your heart is working properly before and during your treatment with this medicine.
- **Blood clots**
MEKTOVI can cause blood clots in your arms or legs which can travel to your lungs and lead to death. If necessary, your doctor may decide to interrupt or completely stop your MEKTOVI treatment.
- **Bleeding problems**
MEKTOVI may cause serious bleeding problems. Tell your doctor immediately if you have any signs of bleeding.
- **Eye problems**
MEKTOVI I may cause serious eye problems. Your doctor will examine your eyes for any new or worsening problems with your sight while you are taking these medicines.
- **Liver problems**
MEKTOVI may increase the amounts of liver enzymes in your blood. Your doctor will run blood tests to monitor your liver function before and during treatment.
- **Muscle problems**
MEKTOVI can cause breakdown of muscle (rhabdomyolysis). Your doctor will run blood tests to monitor muscle condition before and during treatment. As a precaution, drink plenty of fluids during treatment, unless otherwise advised by your doctor.
- **High blood pressure**
MEKTOVI can raise blood pressure. Your doctor or nurse will check your blood pressure before and during treatment with MEKTOVI.
- **Lung or breathing problems**
MEKTOVI may cause lung or breathing problems including inflammation of the lungs (pneumonitis or interstitial lung disease). Signs and symptoms can include: cough, shortness of breath or fatigue. If necessary, your doctor may interrupt or completely stop your MEKTOVI treatment.

Remind any doctor, dentist or pharmacist you visit that you are using MEKTOVI. Keep all of your doctor's appointments so that your progress can be checked.

Things you should not do
- Do not take MEKTOVI to treat any other complaints unless your doctor tells you to.
- Do not give your medicine to anyone else, even if their symptoms seem similar to yours or they have the same condition as you.

- Do not stop taking your medicine or lower the dosage without checking with your doctor

Driving or using machines

Be careful before you drive or use any machines or tools until you know how MEKTOVI affects you.

MEKTOVI can affect your ability to drive or use machines.

If you experience any problems with your vision, or any other side-effects that may affect your ability, avoid driving or using machines. Talk to your doctor if you are not sure if you should drive.

Looking after your medicine
- Keep your MEKTOVI tablets in their original pack until it is time to take them.
- Keep your MEKTOVI tablets in a place where the temperature stays below 30°C.

Follow the instructions in the carton on how to take care of your medicine properly.

Store it in a cool dry place away from moisture, heat or sunlight; for example, do not store it:
- in the bathroom or near a sink, or
- in the car or on window sills.

Keep it where young children cannot reach it.

Getting rid of any unwanted medicine
If your doctor tells you to stop taking this medicine or the expiry date has passed, ask your pharmacist what to do with any medicine that is left over.

Do not throw any medicines away via wastewater or household waste.

6. Are there any side effects?

All medicines can have side effects. If you do experience any side effects, most of them are minor and temporary. However, some side effects may need medical attention.
See the information below and, if you need to, ask your doctor or pharmacist if you have any further questions about side effects.

Less serious side effects

When MEKTOVI was taken with BRAFTOVI the following side effects were reported.

Less serious side effects
Head and neurology related: • problems with nerves that can cause pain, loss of sensation or tingling in hands and feet • headache • dizziness • fever • fatigue • changes in the way things taste • weakness and paralysis of the face muscles (facial paresis) **Bleeding related:** • reduced red blood cell count (anaemia) • bleeding at various sites in the body **Heart related:** • high blood pressure • abnormal blood test results related to blood creatine kinase, indicating damage to the heart and muscle • swelling of the hands or feet (peripheral oedema), localised swelling **Eyes related:** • problems with your vision (visual impairment) • inflammation of the eye (uveitis) **Gastrointestinal related:** • stomach pain • diarrhoea • being sick (vomiting) • feeling sick (nausea) • constipation • abnormal blood test results for liver function • inflammation of the colon (colitis) • kidney failure • abnormal kidney test results (creatinine elevations) • abnormal blood test results for liver function (blood alkaline phosphatase) • abnormal blood test results for pancreas function (amylase, lipase) • inflammation of the pancreas (pancreatitis) causing severe abdominal pain **Muscle related:** • joint pain (arthralgia) • muscle pain (myalgia), weakness or spasm • back pain • pain in the hands and feet **Skin and hair related:** • itching • dry skin • abnormal hair loss or thinning (alopecia) • skin rash of various types • thickening of the outer layers of the skin • some types of benign (non-cancerous) skin tumours such as skin papilloma • type of skin cancer such as basal cell carcinoma • redness, chapping or cracking of the skin • inflammation of the fatty layer under the skin, symptoms include tender skin nodules • skin rash with flat discoloured area or raised bumps like acne (dermatitis acneiform) • redness, skin peeling or blisters on hands and feet (called palmar-plantar erythrodysaesthesia or hand and foot syndrome) • increased skin sensitivity to sunlight
What to do
Speak to your doctor if you have any of these less serious side effects and they worry you.

Serious side effects

Serious side effects
Heart related: MEKTOVI can affect how well your heart pumps (left ventricular dysfunction). Signs and symptoms can include: • feeling dizzy, tired or lightheaded • shortness of breath • feeling like your heart is pounding, racing or beating irregularly • swelling in the legs **Blood pressure related:** MEKTOVI can increase blood pressure. Tell your doctor immediately if you experience severe headache, feel dizzy or lightheaded, or if your blood pressure is much higher than usual (if you are self-monitoring your blood pressure at home). **Blood clot related:** MEKTOVI may cause blood clots (venous thromboembolism including pulmonary embolism). Signs and symptoms can include: • chest pain • sudden shortness of breath or trouble breathing • pain in your legs with or without swelling • swelling in your arms and legs • a cool, pale arm or leg **Eye related:** MEKTOVI may induce fluid leakage under the retina in the eye that results in detachment of different layers in the eye (retinal pigment epithelial detachment), which could lead to the following symptoms: • blurred vision, loss of vision or other vision changes (e.g. coloured dots in your vision) • halo (seeing blurred outline around objects) • eye pain, swelling or redness **Muscle related:** MEKTOVI may lead to breakdown of muscles (rhabdomyolysis) which can lead to kidney damage and can be fatal. Signs and symptoms can include: • muscle pain, cramps, stiffness or spasm • dark urine **Bleeding related:** Taking MEKTOVI can cause serious bleeding problems. Tell your doctor immediately if you have any unusual bleeding or signs of bleeding including: • headaches, dizziness or weakness • coughing up of blood or blood clots • vomit containing blood or that looks like "coffee grounds" • red or black tools that look like tar • passing blood in the urine • stomach (abdominal) pain • unusual vaginal bleeding **Other skin cancers:** MEKTOVI when taken with BRAFTOVI may cause other types of skin cancer **Allergy related:** • allergic reaction that may include swelling of the face and difficulty breathing
What to do
Call your doctor straight away, or go straight to the Emergency Department at your nearest hospital if you notice any of these serious side effects.

Tell your doctor or pharmacist if you notice anything else that may be making you feel unwell.

Other side effects not listed here may occur in some people.

Reporting side effects
Always make sure you speak to your doctor or pharmacist before you decide to stop taking any of your medicines.

7. Product details

This medicine is only available with a doctor's prescription.

What MEKTOVI contains

Active ingredient (main ingredient)	15 mg of binimetinib as the active ingredient
Other ingredients (inactive ingredients)	**Tablet core:** • lactose monohydrate • microcrystalline cellulose • colloidal anhydrous silica • croscarmellose sodium • magnesium stearate **Tablet coating:** • polyvinyl alcohol • macrogol 3350 • titanium dioxide • purified talc • iron oxide yellow • iron oxide black
Potential allergens	Lactose monohydrate

Do not take this medicine if you are allergic to any of these ingredients.

What MEKTOVI looks like
MEKTOVI 15 mg tablets are supplied in blister packs of 84 tablets (7 strips of 12 tablets).

The 15 mg tablets are yellow/dark yellow, unscored biconvex, oval and film-coated, with "A" debossed on one face and "15" on the opposite face.

SINxxxxP

Who distributes MEKTOVI
Zuellig Pharma Pte Ltd
15 Changi North Way #01-01
Singapore 498770

® = Registered Trademark

Pierre Fabre Médicament

Table 3: Treatment-emergent adverse events occurring very commonly (≥10% any grade or ≥2 % grades 3 or 4) in patients receiving Combo 450 mg, Enco 300 mg or vemurafenib in Part 1 of study CMEK162B2301

	Combo 450mg QD N=192 n (%)		Enco 300mg QD N=192 n (%)		Vemurafenib N=186 n (%)	
Grade	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Any event	189 (98.4)	115 (59.9)	191 (99.5)	128 (66.7)	186 (100.0)	118 (63.4)
Nausea	83 (43.2)	3 (1.6)	74 (38.5)	8 (4.2)	65 (34.9)	3 (1.6)
Diarrhoea	71 (37.0)	5 (2.6)	26 (13.5)	3 (1.6)	64 (34.4)	4 (2.2)
Vomiting	58 (30.2)	3 (1.6)	54 (28.1)	9 (4.7)	29 (15.6)	2 (1.1)
Fatigue	56 (29.2)	4 (2.1)	48 (25.0)	1 (0.5)	57 (30.6)	4 (2.2)
Arthralgia	51 (26.6)	1 (0.5)	84 (43.8)	18 (9.4)	83 (44.6)	11 (5.9)
Blood creatine phosphokinase increased	44 (22.9)	13 (6.8)	2 (1.0)	0	4 (2.2)	0
Headache	44 (22.9)	3 (1.6)	53 (27.6)	6 (3.1)	36 (19.4)	1 (0.5)
Constipation	43 (22.4)	0	29 (15.1)	0	12 (6.5)	1 (0.5)
Asthenia	39 (20.3)	3 (1.6)	40 (20.8)	5 (2.6)	35 (18.8)	8 (4.3)
Pyrexia	37 (19.3)	7 (3.6)	30 (15.6)	2 (1.0)	52 (28.0)	0
Abdominal pain	33 (17.2)	5 (2.6)	13 (6.8)	4 (2.1)	13 (7.0)	1 (0.5)
Vision blurred	31 (16.1)	0	4 (2.1)	0	4 (2.2)	0
Anaemia	30 (15.6)	9 (4.7)	12 (6.3)	5 (2.6)	15 (8.1)	5 (2.7)
Gamma-glutamyltransferase increased	29 (15.1)	18 (9.4)	23 (12.0)	10 (5.2)	21 (11.3)	6 (3.2)
Dry skin	28 (14.6)	0	58 (30.2)	0	42 (22.6)	0
Hyperkeratosis	28 (14.6)	1 (0.5)	74 (38.5)	7 (3.6)	54 (29.0)	0
Myalgia	28 (14.6)	0	55 (28.6)	19 (9.9)	34 (18.3)	1 (0.5)
Rash	28 (14.6)	2 (1.0)	40 (20.8)	4 (2.1)	54 (29.0)	6 (3.2)
Alopecia	27 (14.1)	0	108 (56.3)	0	68 (36.6)	0
Dizziness	27 (14.1)	4 (2.1)	11 (5.7)	0	5 (2.7)	0
Abdominal pain upper	23 (12.0)	2 (1.0)	18 (9.4)	2 (1.0)	17 (9.1)	1 (0.5)
Pruritus	23 (12.0)	1 (0.5)	42 (21.9)	1 (0.5)	20 (10.8)	0
Pain in extremity	22 (11.5)	2 (1.0)	43 (22.4)	2 (1.0)	26 (14.0)	2 (1.1)
Alanine aminotransferase increased	21 (10.9)	10 (5.2)	10 (5.2)	2 (1.0)	14 (7.5)	3 (1.6)
Hypertension	21 (10.9)	10 (5.2)	11 (5.7)	6 (3.1)	22 (11.8)	6 (3.2)
Oedema peripheral	21 (10.9)	3 (1.6)	15 (7.8)	0	20 (10.8)	1 (0.5)
Muscle spasms	20 (10.4)	1 (0.5)	6 (3.1)	0	4 (2.2)	0
Nasopharyngitis	20 (10.4)	0	14 (7.3)	0	19 (10.2)	0
Back pain	19 (9.9)	1 (0.5)	29 (15.1)	5 (2.6)	12 (6.5)	3 (1.6)
Insomnia	19 (9.9)	0	35 (18.2)	5 (2.6)	15 (8.1)	0
Palmoplantar keratoderma	18 (9.4)	0	50 (26.0)	3 (1.6)	31 (16.7)	2 (1.1)
Aspartate aminotransferase increased	16 (8.3)	4 (2.1)	8 (4.2)	1 (0.5)	15 (8.1)	3 (1.6)
Decreased appetite	16 (8.3)	0	40 (20.8)	1 (0.5)	36 (19.4)	2 (1.1)
Skin papilloma	15 (7.8)	0	19 (9.9)	0	31 (16.7)	0
Erythema	14 (7.3)	0	25 (13.0)	1 (0.5)	31 (16.7)	1 (0.5)
Palmar-plantar erythrodysaesthesia syndrome	14 (7.3)	0	98 (51.0)	26 (13.5)	26 (14.0)	2 (1.1)
Musculoskeletal pain	11 (5.7)	0	31 (16.1)	6 (3.1)	11 (5.9)	2 (1.1)
Dysgeusia	10 (5.2)	0	22 (11.5)	0	17 (9.1)	0
Hyperglycaemia	9 (4.7)	4 (2.1)	6 (3.1)	4 (2.1)	0	0
Keratosis pilaris	9 (4.7)	0	33 (17.2)	0	43 (23.1)	0
Photosensitivity reaction	7 (3.6)	1 (0.5)	7 (3.6)	0	46 (24.7)	2 (1.1)
Weight decreased	6 (3.1)	0	29 (15.1)	2 (1.0)	20 (10.8)	0
General physical health deterioration	5 (2.6)	4 (2.1)	4 (2.1)	3 (1.6)	9 (4.8)	8 (4.3)
Keratoacanthoma	5 (2.6)	1 (0.5)	13 (6.8)	0	21 (11.3)	6 (3.2)
Metastases to central nervous system	5 (2.6)	3 (1.6)	5 (2.6)	4 (2.1)	3 (1.6)	3 (1.6)
Pain	4 (2.1)	2 (1.0)	12 (6.3)	7 (3.6)	3 (1.6)	0
Pleural effusion	4 (2.1)	4 (2.1)	3 (1.6)	2 (1.0)	2 (1.1)	1 (0.5)
Pruritus generalised	4 (2.1)	0	18 (9.4)	0	19 (10.2)	2 (1.1)
Rash generalised	4 (2.1)	0	13 (6.8)	1 (0.5)	17 (9.1)	8 (4.3)
Rash maculo-papular	4 (2.1)	0	18 (9.4)	1 (0.5)	27 (14.5)	8 (4.3)
Squamous cell carcinoma	2 (1.0)	0	3 (1.6)	0	12 (6.5)	8 (4.3)
Sunburn	0	0	1 (0.5)	0	19 (10.2)	1 (0.5)

A patient ais counted once within each preferred term.
Preferred terms are sorted in descending order of frequency in the 'Combo 450mg QD' column.
MedDRA Version 19.0 was used in the reporting of adverse events.

Table 4: Progression-free survival and confirmed overall response results, cut-off date: 19 May 2016 (independent central review)

	Binimetinib and encorafenib N = 192 (Combo 450)	Encorafenib N = 194 (Enco 300)	Vemurafenib N = 191 (Vem)
PFS			
Number of events (progressive disease (PD)) (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	7.3 (5.6, 8.2)
HR[a] (95% CI) (vs. Vem) P value (stratified log-rank)[b]	0.54 (0.41, 0.71) <0.001		
HR[a] (95 % CI) (vs. Vem) Nominal p-value		0.68 (0.52, 0.90) 0.007	
HR[a] (95% CI) (vs. Enco 300) P value (stratified log-rank)[b]	0.75 (0.56,1.00) 0.051		
Confirmed Overall Responses			
Overall Response Rate, n (%) (95% CI)	121 (63.0) (55.8, 69.9)	98 (50.5) (43.3 , 57.8)	77 (40.3) (33.3, 47.6)
CR, n (%)	15 (7.8)	10 (5.2)	11 (5.8)
PR, n (%)	106 (55.2)	88 (45.4)	66 (34.6)
SD, n (%)	46 (24.0)	53 (27.3)	73 (38.2)
DCR, n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	156 (81.7) (75.4, 86.9)
Duration of Response			
Median, months (95% CI)	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)

CI = confidence interval; CR = complete response; HR = hazard ratio; PR = partial response; SD = stable disease;
DCR = disease control rate (CR+PR+SD+Non-CR/Non-PD; Non- CR/Non-PD applies only to patients without a target lesion who do not achieve CR or have PD); NE = not estimable. PFS = progression-free survival.
[a] Hazard ratio based on a stratified Cox proportional hazard model
[b] Log-rank p-value (2 sided)

Figure 1:
Kaplan-Meier plot of progression-free survival by independent central review (cut-off date: 19 May 2016)

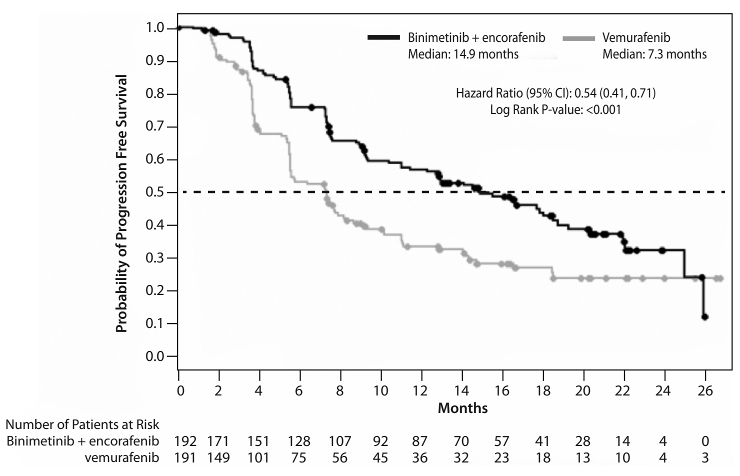


Table 5: Progression-free survival and confirmed overall response results, (cut-off date: 19 May 2016) (investigator assessment)

	Binimetinib and encorafenib N = 192 (Combo 450)	Encorafenib N = 194 (Enco 300)	Vemurafenib N = 191 (Vem)
PFS			
Number of Events (progressive disease (PD))(%)	102 (53.1)	108 (55.7)	121 (63.4)
Median, months (95% CI)	14.8 (10.4, 18.4)	9.2 (7.4,12.9)	7.3 (5.7, 8.5)
HR[a] (95% CI) (vs. Vem) *P* value (stratified log- rank)[b]	0.49 (0.37, 0.64) <0.001		
HR[a] (95% CI) (vs. Enco 300) *P* value (stratified log- rank)[b]	0.68 (0.52, 0.90) 0.006		
Confirmed Overall Responses			
Overall Response Rate (95% CI)	144 (75.0) (68.3, 81.0)	112 (57.7) (50.4, 64.8)	94 (49.2) (41.9, 56.5)
CR, n (%)	31 (16.1)	17 (8.8)	14 (7.3)
PR, n (%)	113 (58.9)	95 (49.0)	80 (41.9)
SD, n (%)	35 (18.2)	55 (28.4)	65 (34.0)
DCR, n (%) (95% CI)	179 (93.2) (88.7, 96.3)	168 (86.6) (81.0, 91.1)	160 (83.8) (77.8, 88.7)

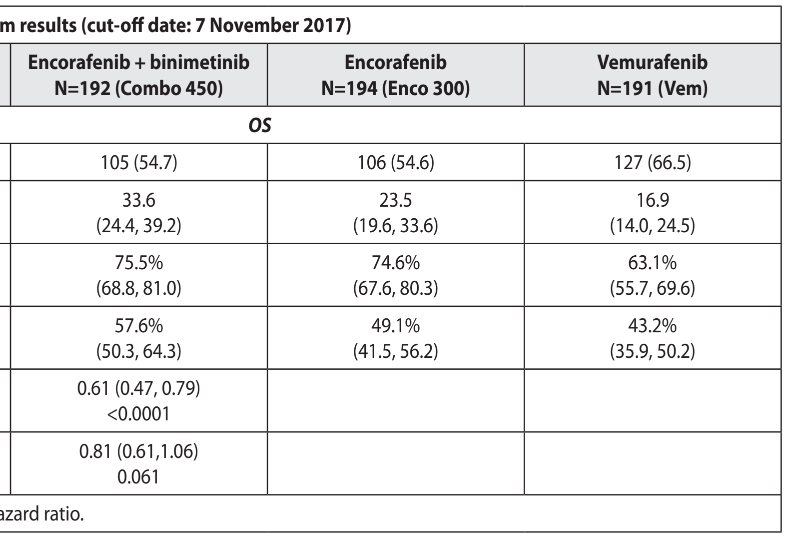
CI = confidence interval; CR = complete response; HR = hazard ratio; PR = partial response; SD = stable disease;
DCR = disease control rate (CR+PR+SD+Non-CR/Non-PD; Non- CR/Non-PD applies only to patients without a target lesion who do not achieve CR or have PD); NE = not estimable. PFS = progression-free survival.
[a] Hazard ratio based on a stratified Cox proportional hazard model
[b] Log-rank p-value (2 sided)

Table 6: Overall survival interim results (cut-off date: 7 November 2017)

	Encorafenib + binimetinib N=192 (Combo 450)	Encorafenib N=194 (Enco 300)	Vemurafenib N=191 (Vem)
OS			
Number of events (%)	105 (54.7)	106 (54.6)	127 (66.5)
Median, months (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Survival at 12 months (95% CI)	75.5% (68.8, 81.0)	74.6% (67.6, 80.3)	63.1% (55.7, 69.6)
Survival at 24 months (95% CI)	57.6% (50.3, 64.3)	49.1% (41.5, 56.2)	43.2% (35.9, 50.2)
HR (95% CI) (vs Vem) p-value (stratified log-rank)	0.61 (0.47, 0.79) <0.0001		
HR (95% CI) (vs Enco 300) p-value (stratified log-rank)	0.81 (0.61,1.06) 0.061		

CI = confidence interval; HR = hazard ratio.

Figure 2:
Kaplan-Meier plot of interim overall survival (cut-off date: 7 November 2017)



in 4.4% of patients. Constipation occurred in 24.1% (66/274) of patients and was Grade 1 or 2. Abdominal pain was reported in 27.4% (75/274) of patients and was Grade 3 in 2.6% (7/274) patients. Nausea occurred in 41.6% (114/274) with Grade 3 or 4 observed in 2.6% (7/274) of patients. Vomiting occurred in 28.1% (77/274) of patients with Grade 3 or 4 reported in 2.2% (6/274) of patients.
Gastrointestinal disorders were typically managed with standard therapy.

Anaemia
In the pooled Combo 450 population, anaemia was reported in 19.7% (54/274) of patients; 4.7% (13/274) of patients had Grade 3 or 4. No patients discontinued treatment due to anaemia, 1.5% (4/274) required dose interruption or dose modification.
In the Combo 300 population of study CMEK162B2301, Part 2, anaemia was observed in 9.7% (25/257) of patients with Grade 3 or 4 reported in 2.7% (7/257) patients.

Headache
In the pooled Combo 450 population, headache occurred in 21.5% (59/274) of patients including Grade 3 in 1.5% (4/274) of patients.
In the Combo 300 population of study CMEK162B2301, Part 2, headache was reported in 12.1% (31/257) of patients and was Grade 3 in 0.4% (1/257) of patients.

Fatigue
In the pooled Combo 450 population, fatigue occurred in 43.8% (120/274) of patients including Grade 3 in 2.9% (8/274) of patients. In the Combo 300 population of study CMEK162B2301, Part 2, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3 or 4 events.

Adverse events
Table 3 summarises adverse events (AEs) occurring at an incidence of ≥ 10% (all grades) or at an incidence of ≥ 2% incidence (grades 3 or 4) and reported in Part 1 of the phase III randomised, active-controlled, open-label, multicentre trial in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma (CMEK162B2301).

Table 3: Treatment-emergent adverse events occurring very commonly (≥ 10% any grade or ≥ 2% grades 3 or 4) in patients receiving Combo 450 mg, Enco 300 mg or vemurafenib in Part 1 of study CMEK162B2301

In Part 1 of study CMEK162B2301, serious adverse events (SAEs) regardless of relationship to study therapy were reported in 35.9% of patients treated with encorafenib 450 mg in combination with binimetinib (Combo 450), 34.9% of patients treated with encorafenib single agent 300 mg (Enco 300) and in 38.2% of patients treated with vemurafenib.

Permanent discontinuations due to AEs were reported in 14.6% of patients treated in the Combo 450 arm, 15.1% of patients treated in the Enco 300 arm and 16.1% of patients treated in the vemurafenib arm.

Special populations

The elderly
In patients treated with Combo 450 (n=274), 194 patients (70.8%) were < 65 years, 65 patients (23.7%) were 65 -74 years and 15 patients (5.5%) were aged > 75. No overall differences in safety or efficacy were observed between elderly patients (≥ 65) and younger patients. The proportion of patients experiencing AEs and SAEs were similar in patients aged < 65 years and those aged > 65 years. The most common AEs reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included diarrhoea, pruritus, GGT and blood phosphatase alkaline elevation. In the small group of patients aged ≥ 75 years (n=15), patients were more likely to experience SAEs and AEs leading to discontinuation of treatment.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at HSA: Healthcare professionals' guide to adverse events reporting.

4.9. OVERDOSE

The highest dose of binimetinib evaluated as single agent in clinical trials was 80 mg administered orally twice daily and was associated with ocular (chorioretinopathy) and skin toxicities (dermatitis acneiform).

In clinical trials of binimetinib in combination with encorafenib, one case of accidental overdose was reported. In this case, a subject took an overdose of 135 mg (9 tablets of binimetinib). No overdose of encorafenib was taken and no adverse events were reported.

Treatment of overdose
There is no specific treatment of overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Since binimetinib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with binimetinib.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action
Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor. ATC code: L01EE03

Binimetinib is an ATP-uncompetitive reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation. In a cell free system, binimetinib inhibits MEK1 and MEK2 with the half maximal inhibitory (IC_{50})'s in the 12-46 nM. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. *In vitro*, binimetinib inhibits MEK-dependant phosphorylation of ERK in human BRAF-mutant melanoma cell lines, significantly inhibiting proliferation and viability of these cell lines. *In vivo*, binimetinib has been evaluated for its ability to inhibit phosphorylation of ERK and tumour growth in xenograft models in nude mice. Additionally, binimetinib has shown significant anti-tumour activity in BRAF-mutant xenograft models, including melanoma. Overall, binimetinib has demonstrated activity against MEK1 and MEK2 enzymes and possesses anti-proliferative activity *in vitro* and *in vivo*.

In non-clinical studies, the combination of binimetinib and encorafenib demonstrated additive or synergistic anti-proliferative activity *in vitro* in numerous BRAF-mutant cell lines. *In vivo*, treatment with the combination resulted in greater anti-tumour activity with respect to tumour growth inhibition and better tumour responses (PR and SD) in BRAFV600E mutant human melanoma xenograft studies in mice than that which was achieved with either agent alone. Additionally, the combination of encorafenib and binimetinib prevented the emergence of treatment resistance in BRAFV600E mutant human melanoma xenografts in mice.

Cardiac electrophysiology
In the safety analysis of pooled studies of encorafenib 450 mg once daily in combination with 45 mg binimetinib twice daily, the incidence of new QTcF prolongation >500 ms was 0.7% (2/268) in the encorafenib 450 mg plus binimetinib group, and 2.5% (5/203) in the encorafenib single agent group. QTcF prolongation of > 60 ms compared to pre-treatment values was observed in 4.9% (13/268) patients in the encorafenib plus binimetinib group, and in 3.4% (7/204) in the encorafenib single agent group (see Sections 4.2 *Dose and method of administration* and 4.4 *Special warnings and special precautions for use* of encorafenib PI).

Clinical trials

BRAF V600 Mutant Unresectable or Metastatic Melanoma
The safety and efficacy of binimetinib in combination with encorafenib were evaluated in a Phase III, randomised (1:1:1) active-controlled, open-label, multicentre trial in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma (CMEK162B2301).
Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to receive prior adjuvant therapy and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior treatment with BRAF/MEK inhibitors was not allowed.

Patients included in the study were randomised to receive binimetinib 45 mg orally twice daily plus encorafenib 450 mg orally once daily (Combo 450, N=192), encorafenib 300 mg orally once daily (Enco 300, N=194), or vemurafenib 960 mg orally twice daily (Vem, N=191). Treatment continued until disease progression or unacceptable toxicity.

Randomisation was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) and prior immunotherapy for unresectable or metastatic disease (yes versus no).

The primary efficacy outcome measure was progression-free survival (PFS) of Combo 450 compared with vemurafenib as assessed by a blinded independent review committee (BIRC). PFS as assessed by investigators (investigator assessment) was a supportive analysis. The key secondary endpoint included PFS of Combo 450 compared with Enco 300. Other secondary efficacy comparisons between Combo 450 and either vemurafenib or Enco 300 included overall survival (OS), objective response rate (ORR), duration of response (DoR) and disease control rate (DCR) as assessed by BIRC and by investigator assessment.

The median age for patients was 56 years (range 20 – 89), 58% were male, 90% were Caucasian, and 72% of patients had baseline ECOG performance status of 0. Most patients had metastatic disease (95%) and were Stage IVM1c (64%); 27% of patients had elevated baseline serum LDH, and 45% of patients had ≥ 3 organs with tumour involvement at baseline and 3.5% had brain metastases.
A total of 27 patients (5%) had received prior checkpoint inhibitors (anti-PD1/PDL1 or ipilimumab) (8 patients in Combo 450 arm, 4%; 7 patients in vemurafenib arm, 4%; 12 patients in Enco 300 arm, 6%) including 22 patients in the metastatic setting (6 patients in Combo 450 arm; 5 patients in vemurafenib arm; 11 patients in Enco 300 arm) and 5 patients in the adjuvant setting (2 patients in Combo 450 arm; 2 patients in vemurafenib arm; 1 patient in Enco 300 arm).
Most patients were BRAF V600E mutant (88.6%), while the remainder were V600K mutant (10.9%).

The median duration of exposure was 11.7 months in patients treated with Combo 450, 7.1 months in patients with encorafenib 300 mg and 6.2 months in patients with vemurafenib. The median relative dose intensity (RDI) for Combo 450 was 99.6% for binimetinib and 100% for encorafenib the median RDI was 86.2% for Enco 300 and 94.5% for vemurafenib.

Study CMEK162B2301 demonstrated a statistically significant improvement in PFS in patients treated with Combo 450 compared with patients treated with vemurafenib. Patients treated with Combo 450 also had improved ORR, DCR, and DoR compared with patients treated with vemurafenib. Table 4 and Figure 1 summarise the PFS and other efficacy results based on central review of the data by the BIRC.

Table 4: Progression-free survival and confirmed overall response results, cut-off date: 19 May 2016 (independent central review)

Figure 1: Kaplan-Meier plot of progression-free survival by independent central review (cut-off date: 19 May 2016)

The efficacy results based on investigator assessment were consistent with the independent central assessment. The results by investigator assessment are summarised in Table 5.

Table 5: Progression-free survival and confirmed overall response results, (cut-off date: 19 May 2016) (investigator assessment)

At a cut-off date of 07 November 2017, an update of the PFS analyses was performed. The PFS analysis per independent central assessment showed an improvement of PFS in patients treated with Combo 450 compared with patients treated with vemurafenib (14.9 vs 7.3 months, respectively), HR 0.51 (95% CI: 0.39, 0.67) (p < 0.001 one sided) and also compared with patients treated with encorafenib (14.9 vs 9.6 months, respectively), HR 0.77 (95% CI: 0.59, 1.0) (p = 0.0249 one sided). The analysis per independent central assessment showed that encorafenib improved PFS vs. vemurafenib (9.6 vs 7.3 months, respectively), HR 0.68 (95% CI: 0.52, 0.88) (p = 0.0019 one sided).

The PFS results per investigator assessment showed consistent results.

An interim OS analysis of study CMEK162B2301 Part 1, performed at the cut-off date of 07 November 2017, demonstrated a statistically significant improvement in OS for Combo 450 compared with vemurafenib (HR 0.61, 95% CI: 0.47, 0.79, [see Table 6 and Figure 2]).
A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4% Combo 450 arm, 36.1% Enco 300 arm, 39.8% vemurafenib arm).

Table 6: Overall survival interim results (cut-off date: 7 November 2017)

Figure 2: Kaplan-Meier plot of interim overall survival (cut-off date: 7 November 2017)

Subgroup analyses of PFS
All subgroup analyses of PFS per BIRC including gender, age (< 65/≥ 65), region (North America, Europe, Australia, other), number of organs involved at baseline (1, 2, 3, > 3), LDH at baseline (<ULN/≥ ULN), ECOG performance status (0/1), AJCC Stage (IIIB, IIIC, IVM1a, IVM1b/IVM1c), and prior adjuvant therapy (Yes/No) demonstrated point estimates in favour of the Combo 450 arm, except for the presence of brain metastases at baseline, a subgroup that only included 12 patients. Most of the HRs in the Combo 450 arm relative to the vemurafenib arm were within the range of the HR observed in the overall population.

Quality of Life (QoL) (Cut-off date: 19 May 2016)
The Functional Assessment of Cancer Therapy-Melanoma (FACT-M), the European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30) and the EuroQoL-5 Dimension-5 Level examination (EQ-5D-5L) were used to explore patient-reported outcomes (PRO) measures of health-related Quality of Life, functioning, melanoma symptoms, and treatment-related side effects. The data showed favourable outcomes for the Combo 450 arm over the vemurafenib arm. The median time to definitive 10% deterioration in the FACT-M score was not reached in the Combo 450 arm and was 22.1 months (95% CI 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI 0.29, 0.72). The median time to definitive 10% deterioration in the EORTC QLQ-C30 global health status score was delayed by more than 7 months in the Combo 450 arm compared to the vemurafenib arm: 23.9 months (95% CI 20.4, NE) vs. 16.6 months (95% CI 11.9, NE) with a HR for the difference of 0.55 (95% CI 0.37, 0.80). As these were exploratory endpoints, they must be interpreted with caution in the context of an open-label study design.

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of binimetinib were studied in healthy subjects and patients with solid tumours and advanced and unresectable or metastatic cutaneous melanoma. After repeated twice-daily dosing concomitantly with encorafenib, steady state concentrations were reached within 15 days with no major accumulation. The mean (CV %) C_{max},ss was 654 ng/mL (34.7 %) and mean AUC_{ss} was 2.35 ug.h/mL (28.0 %) in combination with encorafenib as estimated by population PK modelling. Binimetinib pharmacokinetics have been shown to be approximately dose-linear.

Absorption
After oral administration, binimetinib is rapidly absorbed with a median T_{max} of 1.5 hours. Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, at least 50% of the binimetinib dose was absorbed. Administration of a single 45 mg dose of binimetinib with a high-fat, high-calorie meal decreased the maximum binimetinib concentration (C_{max}) by 17%, while the area under the concentration –time curve (AUC) was unchanged. A drug interaction study in healthy subjects indicated that the extent of binimetinib exposure is not altered in the presence of a gastric pH-altering agent (rabeprazole).

Distribution
Binimetinib is 97.2% bound to human plasma proteins *in vitro*. Binimetinib is distributed to a greater extent in plasma than blood. In humans, the blood-to-plasma ratio is 0.718.
Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, the apparent volume of distribution (Vz/F) of binimetinib is 374 L.

Metabolism
Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, the primary biotransformation pathways of binimetinib observed in humans include glucuronidation, N- dealkylation, amide hydrolysis and loss of ethane-diol from the side chain. The maximum contribution of direct glucuronidation to the clearance of binimetinib was estimated to have been 61.2%. Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, approximately 60% of circulating radioactivity AUC in plasma was attributable to binimetinib. *In vitro*, CYP1A2 and CYP2C19 catalyses the formation of the active metabolite, which represents < 20% of the binimetinib exposure clinically.

Excretion
Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, a mean of 62.3% of the radioactivity was eliminated in the faeces while 31.4% was eliminated in urine. In urine, 6.5% of the radioactivity was excreted as binimetinib. The mean (CV %) apparent clearance (CL/F) of binimetinib was 28.2 L/h (17.5%). The median (range) binimetinib terminal half-life ($T_{1/2}$) was 8.66 h (8.10 to 13.6 h).

Special populations

Hepatic impairment
As binimetinib is primarily metabolised and eliminated via the liver, patients with moderate to severe hepatic impairment may have increased exposure. Results from a dedicated clinical study with binimetinib only indicate similar exposures in patients with mild impairment (Child Pugh Class A) and subjects with normal liver function. A two-fold increase in exposure (AUC) was observed in patients with moderate (Child Pugh Class B) and severe (Child Pugh Class C) hepatic impairment (see section 4.2 *Dose and Method of Administration*). This increase expends to three-fold in both moderate and severe hepatic impairment when considering unbound binimetinib exposure (see section 4.2 *Dose and Method of Administration*).

The effects of hepatic impairment on the pharmacokinetics of binimetinib in combination with encorafenib have not been evaluated clinically.

Gilbert's syndrome
Binimetinib has not been evaluated in patients with Gilbert's disease. The main route of hepatic transformation of binimetinib being glucoronidation, the decision to treat should be made by the treating physician taking into account the individual benefit-risk.

Renal impairment
Binimetinib undergoes minimal renal elimination. Results from a dedicated clinical trial showed that patients with severe renal impairment (eGFR ≤ 29 mL/min/1.73 m²), had a 29% increase in exposure (AUC_{inf}), a 21% increase in C_{max}, and a 22% decrease in CL/F compared to matching healthy subjects. These differences were within the variability observed for these parameters in both cohorts of this study (25% to 49%) and the variability previously observed in patient clinical trials, hence these differences are unlikely to be clinically relevant (see section 4.2 *Dose and Method of Administration*).

The effects of renal impairment on the pharmacokinetics of binimetinib in combination with encorafenib have not been evaluated clinically.

Age/body weight
Based on a population PK analysis, age or body weight do not have a clinically important effect on the systemic exposure of binimetinib.

The elderly
Based on results from a population PK analysis of binimetinib in combination with encorafenib, the pharmacokinetics of binimetinib are similar in elderly patients as compared to younger patients.

Paediatric use
The pharmacokinetics of binimetinib have not been established in children and adolescents below the age of 18 years.

Gender
Based on a population PK analysis, the pharmacokinetics of binimetinib were similar in males as compared with females.

Race
There are insufficient data to evaluate potential differences of race or ethnicity on binimetinib pharmacokinetics.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity
Binimetinib was negative for genotoxicity *in vitro* (reverse mutation in *Salmonella typhimurium* and *E coli* and forward mutation in mouse L5178Y TK+/- lymphoma cells) and *in vivo* (mouse micronucleus assay).

Carcinogenicity
Carcinogenic potential of binimetinib was not evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

The binimetinib drug product is an immediate release film-coated tablet for oral administration. Each tablet contains 15 mg binimetinib. The tablets also contain the excipients: lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate in the tablet core; and polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, iron oxide yellow and iron oxide black in the film coating.

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

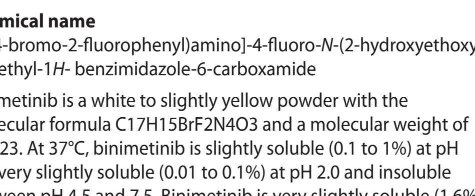
Container type: PVC/PVDC - Aluminium blister containing 12 tablets. Each pack contains 84 tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Singapore, any unused medicine or waste material should be disposed of by taking to your local pharmacy or clinic.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Abstracts Service (CAS) registry number
606143-89-9

Chemical name
5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)-1-methyl-1*H*- benzimidazole-6-carboxamide

Binimetinib is a white to slightly yellow powder with the molecular formula C17H15BrF2N4O3 and a molecular weight of 441.23. At 37°C, binimetinib is slightly soluble (0.1 to 1%) at pH 1.0, very slightly soluble (0.01 to 0.1%) at pH 2.0 and insoluble between pH 4.5 and 7.5. Binimetinib is very slightly soluble (1.6%) in polyethylene glycol, slightly soluble in acetone, acetonitrile, propylene glycol, ethanol and methanol; and very slightly soluble in isopropyl alcohol and n-octanol. Its dissociation constants (pKa) are 2.5 and 8.11. Binimetinib is non-hygroscopic.

7. FORENSIC CLASSIFICATION

Prescription only medicine.

8. NAME AND ADDRESS OF MANUFACTURER

Drug Product Manufacturer
ALMAC Pharma Services Limited
Seagoe Industrial Estate
Portadown
Craigavon
BT63 5UA
United Kingdom (Northern Ireland)

9. PRODUCT OWNER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

10. DATE OF REVISION

February 2022

Pierre Fabre Médicament