Mektovi

BINIMETINIB

Film-Coated Tablets

Reference Label: Belgium/EU-SmPC

Co-marketing agreement with Pierre-Fabre (also the MAH)

AfME Markets using same as LPD: Nigeria

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Mektovi 15 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 15 mg of binimetinib.

Excipient with known effect
Each film-coated tablet contains 133.5 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow to 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 side of the tablet and “15” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRAF V600 Mutant Melanoma
Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see sections 4.4 and 5.1).

BRAF V600E Mutant Metastatic Non-Small Cell Lung Cancer (NSCLC)
Binimetinib in combination with ecorafenib is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation.

4.2 Posology and method of administration

Binimetinib treatment in combination with encorafenib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.

Posology

The recommended dose of binimetinib is 45 mg (three 15 mg tablets) twice daily, corresponding to a total daily dose of 90 mg approximately 12 hours apart.

Dose modification
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation (see below, Table 1 and Table 2).

For patients receiving 45 mg binimetinib twice daily, 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, dose 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.

Dose modifications recommendations in case of adverse reactions are presented below and in Tables 1 and 2.

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 reductions 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. of encorafenib Summary of Product Characteristics (SmPC) for dose modification instructions for encorafenib.

If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption (see Tables 1 and 2) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued.

If encorafenib is temporarily interrupted (see section 4.2 of encorafenib SmPC), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued. For information on the posology and recommended dose modifications of encorafenib, see section 4.2 of encorafenib SmPC.

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

Severity of adverse reaction[a]	**Binimetinib**
Cutaneous reactions	
• Grade2	Binimetinib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, binimetinib should be withheld until improved to Grade 0 or 1 and then resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent Grade2.
• Grade 3	Binimetinib should be withheld until improved to Grade 0 or 1 and resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent Grade 3.
• Grade 4	Binimetinib should be permanently discontinued.
Ocular events	
• Symptomatic retinal pigment epithelial detachments (RPED) (Grade 2 or 3)	Binimetinib should be withheld for up to 2 weeks and ophthalmic monitoring should be repeated including visual acuity assessment. • If improved to Grade 0 or 1, binimetinib should be resumed 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.

Severity of adverse reaction[a]	Binimetinib
• Symptomatic RPED (Grade 4) associated with reduced visual acuity (Grade 4)	Binimetinib should be permanently discontinued.
• Retinal vein occlusion (RVO)	Binimetinib should be permanently discontinued.
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)	LVEF should be evaluated every 2 weeks. • If asymptomatic: Binimetinib should be withheld for up to 4 weeks. Binimetinib should be resumed at a reduced dose if all of the following are present within 4 weeks: o LVEF is at or above the LLN o Absolute decrease from baseline is 10 % or less. • If the LVEF does not recover within 4 weeks, binimetinib should be permanently discontinued.
• Grade 3 or 4 LVEF decrease or symptomatic left ventricular dysfunction (LVD)	Binimetinib should be permanently discontinued. LVEF should be evaluated every 2 weeks until recovery.
Rhabdomyolysis/Creatine phosphokinase (CK) elevation	
• Grade 3 (CK > 5 – 10x upper limit of normal (ULN)) asymptomatic	Binimetinib dose should be maintained and it should be ensured that patient is adequately hydrated.
• Grade 4 (CK > 10x ULN) asymptomatic	Binimetinib should be withheld until improved to Grade 0 or 1. It should be ensured that patient has adequate hydration.
• Grade 3 or grade 4 (CK > 5x ULN) with muscle symptoms or renal impairment	Binimetinib should be withheld until improved to Grade 0 or 1. • If resolved within 4 weeks, binimetinib should be resumed at a reduced dose, or • Binimetinib should be permanently discontinued.
Venous thromboembolism (VTE)	
• Uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) ≤ Grade 3	Binimetinib should be withheld. • If improved to Grade 0 or 1, binimetinib should be resumed at a reduced dose, or • If not improved, binimetinib should be permanently discontinued.
• Grade 4 PE	Binimetinib should be permanently discontinued.

Severity of adverse reaction[a]	Binimetinib
Liver laboratory abnormalities	
• Grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x – ≤ 5x upper limit of normal (ULN)	Binimetinib dose should be maintained. If no improvement within 2 weeks, binimetinib should be withheld until improved to Grade 0 or 1 or to baseline levels, and then resumed at the same dose.
• First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, binimetinib should be resumed at reduced dose, or • If not improved, binimetinib should be permanently discontinued.
• First occurrence of Grade 4 (AST or ALT > 20 ULN)	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, binimetinib should be resumed at a reduced dose level, or • If not improved, binimetinib should be permanently discontinued. Or, binimetinib should be permanently discontinued.
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue binimetinib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Binimetinib should be permanently discontinued.
Interstitial lung disease (ILD)/pneumonitis	
• Grade 2	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1, binimetinib should be resumed at reduced dose, or • If not resolved within 4 weeks, binimetinib should be permanently discontinued.
• Grade 3 or Grade 4	Binimetinib should be permanently discontinued.

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

Table 2: Recommended dose modifications for binimetinib (used in combination with encorafenib) for other adverse reactions

Severity of adverse reaction	Binimetinib
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, binimetinib should be resumed at reduced dose, or • If not improved, binimetinib should be permanently discontinued.
• First occurrence of Grade 4 adverse reactions	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, binimetinib should be resumed at a reduced dose level, or • If not improved, binimetinib should be permanently discontinued. Or, binimetinib should be permanently discontinued binimetinib.
• Recurrent Grade 3 adverse reactions	It should be considered to permanently discontinue binimetinib.
• Recurrent Grade 4 adverse reactions	Binimetinib should be permanently discontinued.

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

Missed doses
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
In case of vomiting after administration of binimetinib, the patient should not re-take the dose and should take the next scheduled dose.

Special populations

Elderly patients
No dose adjustment is required for patients aged 65 years and older (see section 5.2).

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 of encorafenib SmPC).

Renal impairment
No dose adjustment is recommended for patients with renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of binimetinib in children and adolescents have not yet been established. No data are available.

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Method of administration

Mektovi is for oral use.
The tablets are to be swallowed whole with water. They may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Binimetinib is to be given in combination with encorafenib. For additional information on warnings and precautions associated with encorafenib treatment, see section 4.4 of encorafenib SmPC.

BRAF mutation testing

Before taking binimetinib in combination with encorafenib, patients must have BRAF V600 mutation confirmed by validated test. The efficacy and safety of binimetinib in combination with encorafenib have been established only 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 for use of the combination of binimetinib with encorafenib in patients who have progressed on a prior BRAF inhibitor given for the treatment of unresectable or metastatic melanoma with 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 with the combination of binimetinib and encorafenib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain (see section 5.1).

Left ventricular dysfunction (LVD)

LVD defined as symptomatic or asymptomatic decreases in ejection fraction can occur when binimetinib is administered.
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 treatment interruption, dose reduction or with treatment discontinuation (see section 4.2).

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 left ventricular dysfunction, Grade 3-4 LVEF, or absolute decrease of LVEF from baseline of ≥ 10 %, binimetinib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Haemorrhage

Haemorrhages, including major haemorrhagic events, can occur when binimetinib is administered (see section 4.8). 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

interruption, reduction or treatment discontinuation (see Table 2 in section 4.2) and as clinically indicated.

Ocular toxicities

Ocular toxicities including RPED and RVO can occur when binimetinib is administered. Uveitis including iridocyclitis and iritis have been reported in patients treated with binimetinib in combination with encorafenib (see section 4.8).

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. Therefore, binimetinib should 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 treatment interruption, dose reduction or with treatment discontinuation (see Table 1 in section 4.2).
Binimetinib should be permanently discontinued with the occurrence of RVO (see Table 1 in section 4.2).

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

CK elevation and rhabdomyolysis

Asymptomatic CK elevations are seen in patients treated with binimetinib (see section 4.8), and, rhabdomyolysis was uncommonly reported. Special attention should be paid to 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 Table 1 in section 4.2).

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 2 in section 4.2).

Venous thromboembolism (VTE)

VTE can occur when binimetinib is administered (see section 4.8). Binimetinib should be used with caution in patients who are at risk for, or who have a history of VTE.
If during treatment patient develops VTE or pulmonary embolism, it should be managed with dose interruption, reduction or treatment discontinuation (see Table 1 in section 4.2).

Pneumonitis/Interstitial lung disease

Pneumonitis/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). Binimetinib should be permanently discontinued in patients diagnosed with treatment related pneumonitis or ILD.

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 (see section 4.8).

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. Binimetinib and encorafenib 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 (CT) 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 develops 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.

Liver laboratory abnormalities

Liver laboratory abnormalities including AST and ALT elevations can occur with binimetinib (see section 4.8). Liver laboratory values should be monitored before initiation of binimetinib and encorafenib and at least monthly during the 6 first months of treatment, and then as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see Table 1 in section 4.2).

Hepatic impairment

Liver metabolism mainly via glucuronidation is the primary route of elimination of binimetinib (see section 5.2). 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 and 5.2).

Lactose intolerance

Mektovi contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on binimetinib

Binimetinib is primarily metabolised through UGT1A1 mediated glucuronidation. The extent of drug interactions mediated by UGT1A1 is unlikely to be clinically relevant (see section 5.2); however, as

this has not been evaluated in a formal clinical study, UGT1A1 inducers (such as rifampicin and phenobarbital) and inhibitors (such as indinavir, atazanavir, sorafenib) should be co-administered with caution.

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 (see section 5.2*)*.

Inducers of CYP1A2 enzymes (such as carbamazepine and rifampicin) and inducers of Pgp transport (such as Saint John's wort or phenytoin) may decrease binimetinib exposure, which could result in a decrease of efficacy.

Effects of binimetinib on other medicinal products

Binimetinib is a potential inducer of CYP1A2, and caution should be taken when it is used with sensitive substrates (such as duloxetine or theophylline).

Binimetinib is a weak inhibitor of OAT3, and caution should be taken when it is used with sensitive substrates (such as pravastatin or ciprofloxacin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential must use effective contraception during treatment with binimetinib and for at least 1 month following the last dose.

Pregnancy

There are no data from the use of binimetinb in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Binimetinib is not recommended during pregnancy and in women of childbearing potential not using contraception. If binimetinib is used during pregnancy, or if the patient becomes pregnant while taking binimetinib, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is unknown whether binimetinib or its metabolite are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Mektovi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

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

4.7 Effects on ability to drive and use machines

Binimetinib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in patients treated with binimetinib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reaction that may affect their ability to drive and use machines (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of safety profile

The safety of binimetinib (45 mg orally twice daily) in combination with encorafenib (450 mg orally once daily) (hereafter referred to as Combo 450) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma, based on two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, Part 1) (hereafter referred to as the pooled Combo 450 population). At the recommended dose (n = 274) in patients with unresectable or metastatic melanoma, the most common adverse reactions (≥ 25 %) occurring in patients treated with binimetinib administered 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 list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and the following frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: 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)
Neoplasms benign, malignant and unspecified	Cutaneous squamous cell carcinoma[a]	Common
	Basal cell carcinoma[*]	Common
	Skin papilloma[*]	Common
Blood and lymphatic system disorders	Anaemia	Very common
Immune system disorders	Hypersensitivity[b]	Common
Nervous system disorders	Neuropathy peripheral[*]	Very common
	Dizziness[*]	Very common
	Headache[*]	Very common
	Dysgeusia	Common
	Facial paresis[c]	Uncommon
Eye disorders	Visual impairment[*]	Very common
	RPED[*]	Very common
	Uveitis[*]	Common
Cardiac disorders	Left ventricular dysfunction[d]	Common
Vascular disorders	Haemorrhage[e]	Very common
	Hypertension[*]	Very common
	Venous thromboembolism[f]	Common

Gastrointestinal disorders	Abdominal pain*	Very common
	Diarrhoea*	Very common
	Vomiting*	Very common
	Nausea	Very common
	Constipation	Very common
	Colitis[g]	Common
	Pancreatitis*	Uncommon
Skin and subcutaneous tissue disorders	Hyperkeratosis *	Very common
	Rash *	Very common
	Dry skin*	Very common
	Pruritus*	Very common
	Alopecia*	Very common
	Photosensitivity*	Common
	Dermatitis acneiform*	Common
	Palmar-plantar erythrodysaesthesia syndrome (PPES)	Common
	Erythema*	Common
	Panniculitis*	Common
Musculoskeletal and connective tissue disorders	Arthralgia*	Very common
	Muscular disorders/Myalgia[h]	Very common
	Back pain	Very common
	Pain in extremity	Very common
	Rhabdomyolysis	Uncommon
Renal and urinary disorders	Renal failure*	Common
General disorders and administration site conditions	Pyrexia*	Very common
	Peripheral oedema [i]	Very common
	Fatigue*	Very common
Investigations	Blood creatine phosphokinase increased	Very Common
	Transaminase increased*	Very Common
	Gamma-glutamyl transferase increased*	Very Common
	Blood creatinine increased*	Common
	Blood alkaline phosphatase increased	Common
	Amylase increased	Common
	Lipase increased	Common

*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, hypersensitivity vasculitis and urticaria

[c] includes facial nerve disorder, facial paralysis, facial paresis

[d] includes left ventricular dysfunction, ejection fraction decreased, cardiac failure and ejection fraction abnormal

[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

When encorafenib was used at a dose of 300 mg once daily in combination with binimetinib 45 mg twice daily (Combo 300) in study CMEK162B2301-Part 2, the frequency category was lower compared to the pooled Combo 450 population for the following adverse reactions: anemia, peripheral

neuropathy, haemorrhage, hypertension, pruritus (common) and colitis, increased amylase and increased lipase (uncommon).

Description of selected adverse reactions

Cutaneous malignancies
CuSCC was reported when binimetinib was used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

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) of patients and Grade 3 in 1.8 % (5/274) of patients. Most events were reported as retinopathy, retinal detachment, subretinal fluid, macular oedema, and chorioretinopathy 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).
Visual impairment, including vision blurred and reduced visual acuity, occurred in 21.5 % (59/274) of patients. Visual impairment was generally reversible.
Uveitis was also reported when binimetinib was used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

In Study CMEK162B2301-Part 2, in the Combo 300 arm, RPED was observed in 12.5% (32/257) of patients with 0.4% (1/257) Grade 4 event.

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 were 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 requiring 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.

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. Hypertension 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 patients treated with Combo 450, VTE occurred in 4.7 % (13/274) of patients, including 2.2 % (6/274) of patients who developed pulmonary embolism. In the pooled Combo 450 population, 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 of encorafenib SmPC).

Dermatologic reactions
Dermatologic reactions may occur when binimetinib is used in combination with encorafenib.

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

Dermatitis acneiform
In patients treated with Combo 450, dermatitis acneiform occurred in 4.4 % (12/274) of patients, was Grade 1 and 2 and no event led to treatment discontinuation. Dose modification was reported in 0.7 % (2/274) of patients.

Palmar-plantar erythrodysaesthesia syndrome
PPES can occur when binimetinib is used in combination with encorafenib (see section 4.8 of encorafenib SmPC).

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 of encorafenib SmPC).

CK elevation/rhabdomyolysis
In the pooled Combo 450 population, mostly mild asymptomatic blood CK elevation was reported in 27.0 % (74/274) of patients. The incidence of Grade 3 or 4 adverse reactions 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 of encorafenib SmPC).

Liver laboratory abnormalities
The incidences of liver laboratory abnormalities reported in the pooled Combo 450 population are listed below:

- Increased transaminases: 15.7% (43/274) overall – Grade 3-4: 5.5% (15/274)
- Increased GGT: 14.6% (40/274) overall – Grade 3-4: 8.4% (23/274)

In Study CMEK162B2301-Part 2, in the Combo 300 arm, the incidences of liver laboratory abnormalities are listed below:

- Increased transaminases: 13.2% (34/257) overall – Grade 3-4: 5.4% (14/257)
- Increased GGT: 14.0% (36/257) overall – Grade 3-4: 4.7% (12/257)

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 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.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, nausea was observed in 27.2% (70/257) of patients and was Grade 3 in 1.6% (4/257) of patients. Vomiting occurred in 15.2% (39/257) of patients with Grade 3 reported in 0.4% (1/257) of patients. Diarrhoea occurred in 28.4% (73/257) of patients with Grade 3 reported in 1.6% (4/257) 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 Study CMEK162B2301-Part 2, in the Combo 300 arm, anaemia was observed in 9.7% (25/257) of patients with Grade 3-4 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 Study CMEK162B2301-Part 2, in the Combo 300 arm, 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 Study CMEK162B2301-Part 2, in the Combo 300 arm, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3-4 events.

Special populations

Elderly

In patients treated with Combo 450 (n = 274), 194 patients (70.8 %) were < 65 years old, 65 patients (23.7 %) were 65 -74 years old 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 adverse events and serious adverse events were similar in patients aged <65 years and those aged ≥ 65 years. The most common adverse events 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 serious adverse events and adverse events leading to discontinuation of treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing 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 according to their local requirements.

4.9 Overdose

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

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, haemodialysis is likely to be ineffective in the treatment of overdose with binimetinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EE03

Mechanism of action

Binimetinib is an ATP-uncompetitive, reversible inhibitor of the kinase activity of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. In cell free system, binimetinib inhibits MEK1 and MEK2 with the half maximal inhibitory concentration (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 melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activates MEK. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. Binimetinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma animal models.

Combination with encorafenib

Binimetinib and encorafenib (a BRAF inhibitor, see section 5.1 of encorafenib SmPC) both inhibit the MAPK pathway resulting in higher anti-tumour activity.
Additionally, the combination of encorafenib and binimetinib prevented the emergence of treatment resistance in BRAF V600E mutant human melanoma xenografts *in vivo*.

Clinical efficacy and safety

BRAF V600 mutant unresectable or metastatic melanoma
The safety and efficacy of binimetinib in combination with encorafenib were evaluated in a 2-part Phase III, randomised (1:1:1) active-controlled, open-label, multicenter study in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma (Study CMEK162B2301), as detected using a BRAF assay. Patients had histologically confirmed cutaneous or unknown primary melanoma but those with uveal or mucosal melanoma were excluded. 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.

Study CMEK162B2301, Part 1

In part 1, patients in the study were randomised to receive binimetinib 45 mg orally twice daily plus encorafenib 450 mg orally daily (Combo 450, n = 192), encorafenib 300 mg orally daily (hereafter referred to as Enco 300, n = 194), or vemurafenib 960 mg orally twice daily (hereafter referred to as 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, vs IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and prior immunotherapy for unresectable or metastatic disease (yes vs 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. An additional 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 of 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 lactate dehydrogenase (LDH), and 45% of patients had at least 3 organs with tumour involvement at baseline and 3.5 % had brain metastases. 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.

The median duration of exposure was 11.7 months in patients treated with Combo 450, 7.1 months in patients treated with encorafenib 300 mg and 6.2 months in patients treated 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.

Part 1 of study CMEK162B2301 demonstrated a statistically significant improvement in PFS in the patients treated with Combo 450 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 a blinded independent radiology committee.

The efficacy results based on investigator assessment were consistent with the independent central assessment. Unstratified subgroup analyses demonstrated point estimates in favour of Combo 450, including LDH at baseline, ECOG performance status and AJCC stage.

Table 4: Study CMEK162B2301, Part 1: Progression-free survival and confirmed overall response results (independent central review)

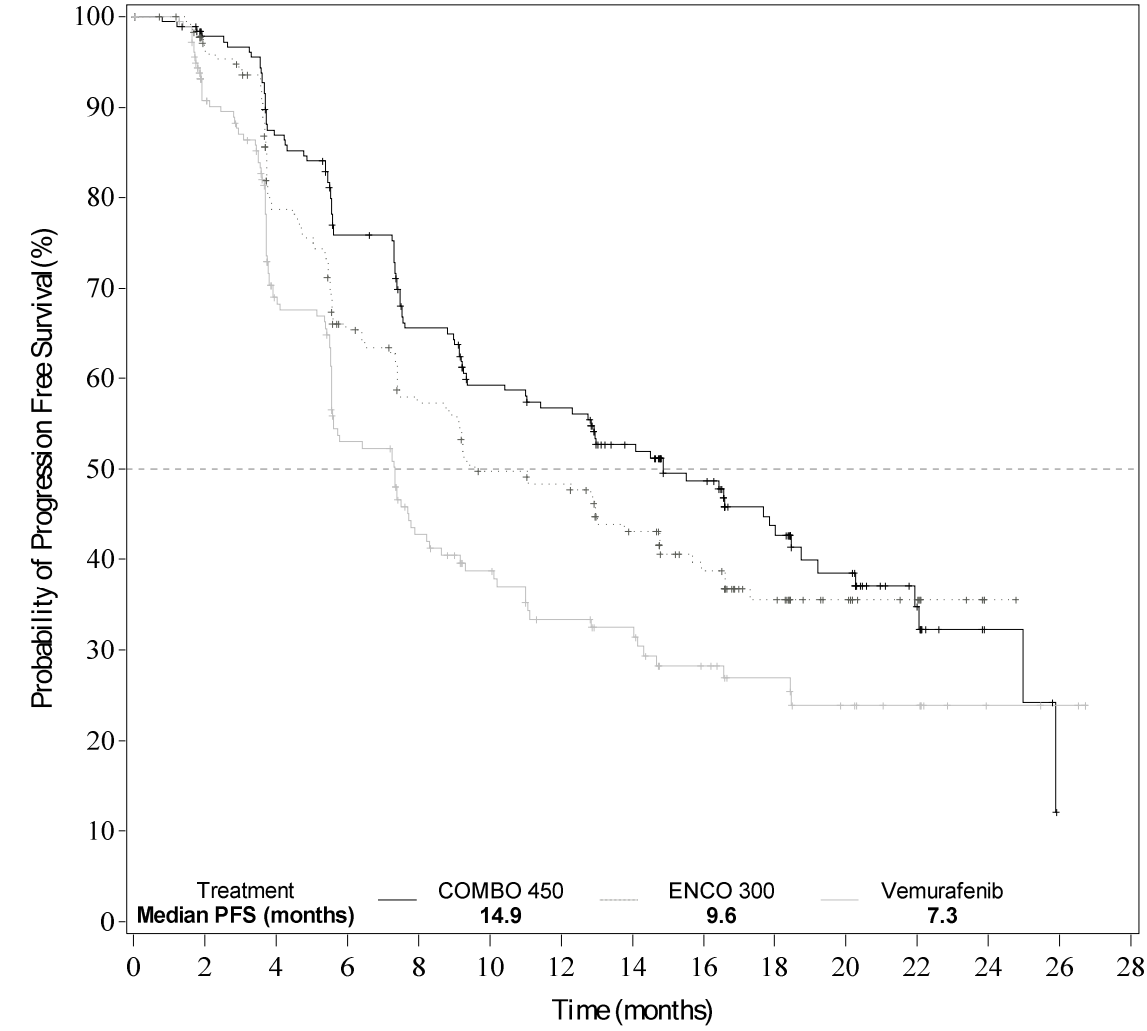
	Encorafenib + binimetinib n = 192 (Combo 450)	**Encorafenib n = 194 (Enco 300)**	**Vemurafenib n = 191 (Vem)**
Cut-off date: 19 May 2016			
PFS (primary analysis)			
Number of events (progressive disease(PD)) (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95 % CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	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)
Updated analysis, cut-off date: 07 November 2017			
PFS			
Number of events (progressive disease) (%)	113 (58.9)	112 (57.7)	118 (61.8)
Median, months (95% CI)	14.9 (11.0, 20.2)	9.6 (7.4,14.8)	7.3 (5.6, 7.9)
HR[a] (95% CI) (vs Vem) Nominal p-value	0.51 (0.39, 0.67) <0.001		
HR[a] (95% CI) (vs Vem) Nominal p-value		0.68 (0.52, 0.88) 0.0038	
HR[a] (95% CI) (vs Enco 300) Nominal p-value	0.77 (0.59,1.00) 0.0498		

CI = confidence interval; CR = complete response; DCR = disease control rate (CR+PR+SD+Non-CR/Non-PD; Non-CR/Non-PD applies only to patients without a target lesion who did not achieve CR or have PD); HR = hazard ratio; NE = not estimable; PFS = progression-free survival; PR = partial response; SD = stable disease. Vem = vemurafenib.

[a] Hazard ratio based on a stratified Cox proportional hazard model

[b] Log-rank p-value (2-sided)

Figure 1: Study CMEK162B2301, Part 1: Kaplan-Meier plot of progression-free survival by independent central review (cut-off date 19 May 2016)

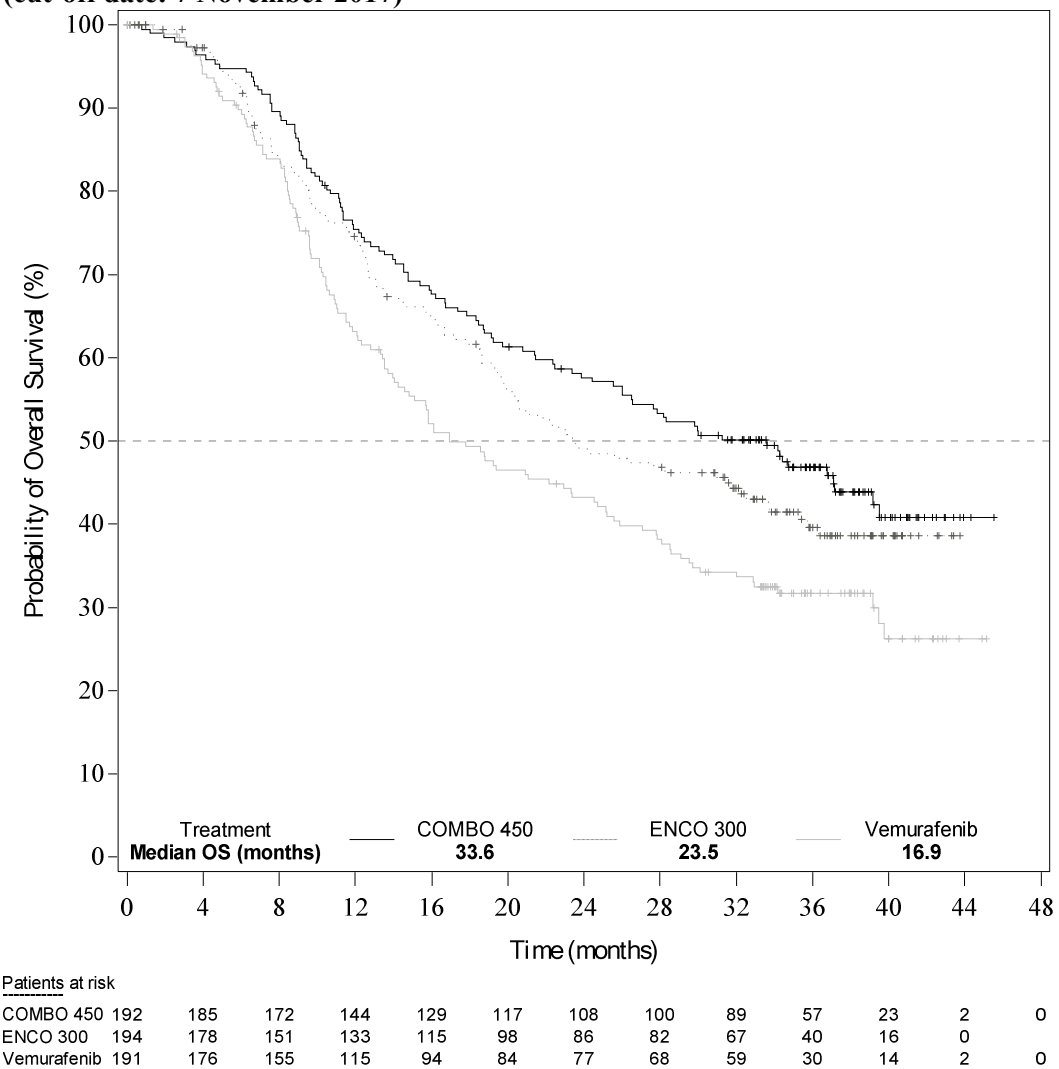


An interim OS analysis of study CMEK162B2301 Part 1, (cut-off date 07 November 2017) demonstrated a statistically significant improvement in OS for Combo 450 compared with vemurafenib (see Table 5 and Figure 2).
A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4 % Combo 450 arm, 36.1 % encorafenib arm, 39.8 % vemurafenib arm).

Table 5: Study CMEK162B2301, Part 1: 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[a] (95 % CI) (vs Vem) p-value (stratified log-rank)	0.61 (0.47, 0.79) < 0.0001		
HR[a] (95 % CI) (vs. Enco 300) p-value (stratified log-rank)	0.81 (0.61,1.06) 0.061		

Figure 2 Study CMEK162B2301, Part 1: Kaplan-Meier plot of interim overall survival (cut-off date: 7 November 2017)



Quality of Life (QoL) (cut-off date: 19 May 2016)
The Functional Assessment of Cancer Therapy-Melanoma (FACT-M), the European Organisation 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 adverse reaction. A definitive 10% deterioration in FACT-M and in EORTC QLQ-C30 was significantly delayed in patients treated with Combo 450 relative to other treatments. 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). An analysis of time to definitive 10 % deterioration in EORTC QLQ-C30 score provided with similar results.
Patients receiving Combo 450 reported no change or a slight improvement in the mean change from baseline EQ-5D-5L index score at all visits, whilst patients receiving vemurafenib or encorafenib reported decreases at all visits (with statistical significant differences). An evaluation of change over time in score yielded the same trend for EORTC QLQ-C30 and at all visit for FACT-M.

Study CMEK162B2301, Part 2
Part 2 of study CMEK162B2301 was designed to assess the contribution of binimetinib to the encorafenib and binimetinib combination.
The PFS for encorafenib 300 mg orally daily used in combination with binimetinib 45 mg orally twice daily (Combo 300, n = 258) was compared to the PFS for Enco 300 (n = 280, including 194 patients from Part 1 and 86 patients from Part 2). Enrolment in Part 2 started after all Part 1 patients were randomised.

Preliminary Part 2 data at a cut-off date of 9 November 2016 demonstrated the contribution of binimetinib with an improved median PFS estimate of 12.9 months (95 % CI: 10.1, 14.0) for Combo 300 compared to 9.2 months (95 % CI: 7.4, 11.0) for Enco 300 (Parts 1 and 2) per independent central review (BIRC). Similar results were observed per Investigator assessment.
The confirmed ORR per BIRC was 65.9 % (95 % CI: 59.8, 71.7) for Combo 300, and 50.4 % (95 % CI 44.3, 56.4) for Enco 300 (Parts 1 and 2). Median DOR for confirmed responses per BIRC was 12.7 months [95% CI: 9.3, 15.1] for Combo 300 and 12.9 months [95 % CI: 8.9, 15.5] for Enco 300. The median duration of treatment was longer for Combo 300 vs. Enco 300, 52.1 weeks vs 31.5 weeks.

Cardiac electrophysiology
In the safety analysis of pooled studies of encorafenib 450 mg once daily in combination with 45 mg binimetinib twice daily (Combo 450), the incidence of new QTc 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. QTc 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 section 5.1 of encorafenib SmPC).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with binimetinib in one or more subsets of the paediatric population in melanoma (see section 4.2 for information on paediatric use).

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 repeat twice-daily dosing concomitantly with encorafenib, steady-state conditions for binimetinib 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 more distributed 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.

Biotransformation

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 the circulating radioactivity AUC in plasma was attributable to binimetinib. *In vitro*, CYP1A2 and CYP2C19 catalyse the formation of the active metabolite, which represents less than 20 % of the binimetinib exposure clinically.

Elimination

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 feces while 31.4 % was eliminated in the 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).

Medicinal product interactions

Effect of UGT1A1 inducers or inhibitors on binimetinib
Binimetinib is primarily metabolised through UGT1A1 mediated glucuronidation. In 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. Therefore, the extent of drug interactions mediated by UGT1A1 is minimal, and unlikely clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 inducers or inhibitors should be administered with caution.

Effect of CYP enzymes on binimetinib
In vitro, CYP1A2 and CYP2C19 catalyse the formation of the active metabolite, AR00426032 (M3) by oxidative N-desmethylation.

Effect of binimetinib on CYP substrates
Binimetinib is a weak reversible inhibitor of CYP1A2 and CYP2C9.

Effect of transporters on binimetinib
In vitro experiments indicate that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Inhibition of P-gp or BCRP is unlikely to result in a clinically important increase in binimetinib concentrations as binimetinib exhibits moderate to high passive permeability.

Effect of binimetinib on transporters
Binimetinib is a weak inhibitor of OAT3. No clinicallly significant drug-drug interactions caused by binimetinib on other transporters is expected.

Binimetinib is metabolised by UGTs and CYP1A2 and is a substrate for Pgp. Specific inducers of these enzymes have not been studied and may result in a loss of efficacy.

Special populations

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

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

Race
There are insufficient data to evaluate potential differences in the exposure of binimetinib by race or ethnicity.

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 total binimetinib exposure (AUC) was observed in patients with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment (see section 4.2). This increase expends to three fold in both moderate and severe hepatic impairment when considering unbound binimetinib exposure (see section 4.2).

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 for treatement 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 study showed that patients with severe renal impairment (eGFR ≤ 29 mL/min/1.73 m^2), 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 % - 49 %) and the variability previously observed in patient clinical studies, hence these differences are unlikely to be clinically relevant.

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

5.3 Preclinical safety data

Repeated oral administration of binimetinib in rats for up to 6 months was associated with soft tissue mineralisation, gastric mucosal lesions and reversible minimal to mild clinical pathology changes at 7 to 12.5 times human therapeutic exposures. In a gastric irritation study in rats, an increased incidence of superficial mucosal lesions and of hemorrhagic ulcers were observed. In cynomolgus monkeys, oral

administration of binimetinib was associated with gastro-intestinal intolerance, moderate clinical pathology changes, bone marrow hypercellularity and microscopic findings of gastrointestinal inflammation, reversible at the lowest doses which were below human therapeutic exposures.

Carcinogenic potential of binimetinib was not evaluated. Standard genotixicity studies with binimetinib were negative.

The potential embryo-foetal effects of binimetinib were evaluated in rats and rabbits. In rats, lower gestational body weight gain and fetal body weights and a decreased number of ossified fetal sternebrae were noted. No effects were noted at 14-times the human therapeutic exposure .
In rabbits, mortality, maternal physical signs of toxicity, lower gestational body weight and abortion were noted. The number of viable foetuses and foetal body weights were reduced and post-implantation loss and resorptions were increased. An increased litter incidence of foetal ventricular septal defects and pulmonary trunk alterations was noted at the highest doses. No effects were observed at 3times the human therapeutic exposure.

Fertility studies were not conducted with binimetinib. In repeat-dose toxicity studies, no concern in terms of fertility was raised from pathological examination of reproductive organs in rats and monkeys.

Binimetinib has phototoxic potential *in vitro*.
A minimal risk for photosensitisation was shown *in vivo* at an oral dose providing 3.8-fold higher exposure than that achieved with the recommended dose in humans. These data indicate that there is minimal risk for phototoxicity with binimetinib at therapeutic doses in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Cellulose microcrystalline (E460i)
Silica colloidal anhydrous (E551)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Film-coating
Polyvinyl alcohol (E1203)
Macrogol 3350 (E1521)
Titanium dioxide (E171)
Talc (E533b)
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use Mektovi after the expiry date which is stated on the Carton/Blister after “EXP”:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Alu blister containing 12 tablets. Each pack contains either 84 or 168 tablets**.**
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

MANUFACTURED BY:

Almac Pharma Services Limited
Seagoe Industrial Estate - Portadown - Craigavon - BT63 5UA, UK

PACKAGED AND RELEASED BY:

Pierre Fabre Médicament Production Site
PROGIPHARM - Rue du Lycée, 45500 GIEN, France

8. PRESCRIPTION STATUS

Prescription only medicine

9. DATE OF REVISION OF THE TEXT

November 2023

Document Approval Record

Document Name:	Mektovi 15 mg FCT LPD Nigeria (Pierre Fabre)
Document Title:	Mektovi 15 mg FCT LPD Nigeria (USPI - LAB-1426-2.0 - New Indication (NSCLC 1L) Only)

Signed By:	Date(GMT)	Signing Capacity
Ongare, Louise Akeyo	16-Nov-2023 09:13:35	Regulatory Affairs Approval