ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mektovi 15 mg film-coated tablets
Mektovi 45 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mektovi 15 mg film-coated tablets
Each film-coated tablet contains 15 mg of binimetinib.
Excipient with known effect
Each film-coated tablet contains 133.5 mg of lactose monohydrate.

Mektovi 45 mg film-coated tablets
Each film-coated tablet contains 45 mg of binimetinib.
Excipient with known effect
Each film-coated tablet contains 234.9 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Mektovi 15 mg film-coated tablets
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.

Mektovi 45 mg film-coated tablets
White to off-white, unscored biconvex, ovaloid film-coated tablets approximately 15 mm in length and 6 mm in width, with "45" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Non-small cell lung cancer (NSCLC)

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer 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.

BRAF mutation testing

Before taking binimetinib in combination with encorafenib, patients must have confirmation of BRAF V600E mutation assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

The efficacy and safety of binimetinib in combination with encorafenib have been established only in patients with melanoma tumours expressing BRAF V600E and V600K mutations, or NSCLC expressing a BRAF V600E mutation. Binimetinib in combination with encorafenib should not be used in patients with wild type BRAF malignant melanoma or wild type BRAF NSCLC.

Posology

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

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.
• 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.

Severity of adverse reaction[a]	Binimetinib
• 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.
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.
• 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.

.

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.

For patients unable to swallow, Mektovi 15 mg tablets may be dispersed in a small glass (approximately 10 mL) of either water, orange juice or apple juice and taken immediately. The glass should be rinsed with approximately 10 mL of water, orange juice or apple juice, and content drunk immediately.

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.

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 or BRAF V600E mutant NSCLC 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.

Tumour lysis syndrome (TLS)

The occurrence of TLS, which may be fatal, has been associated with the use of binimetinib in association with encorafenib (see section 4.8). Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

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 breastfed 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) has been evaluated in the integrated safety population (ISP) of 372 patients including patients with BRAF V600 mutant unresectable or metastatic melanoma and BRAF V600E mutant advanced NSCLC (hereafter referred to as Combo 450 ISP). In Combo 450 ISP, 274 patients received the combination for the treatment of BRAF V600 mutant unresectable or metastatic melanoma (in two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, Part 1), and 98 received the combination for the treatment of BRAF V600E mutant advanced NSCLC (in one non-randomized Phase II study (ARRAY-818-202)) (see section 5.1).
The most common adverse reactions (≥ 25 %) occurring in patients treated with binimetinib administered with encorafenib were fatigue, nausea, diarrhoea, vomiting, abdominal pain, myopathy/muscular disorders and arthralgia.

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 = 372)

System Organ Class	Adverse reaction	Frequency (All grades)
Neoplasms benign, malignant and unspecified	Cutaneous squamous cell carcinoma[a]	Common
	Skin papilloma[*]	Common
	Basal cell carcinoma[*]	Uncommon
Blood and lymphatic system disorders	Anaemia	Very common
Immune system disorders	Hypersensitivity[b]	Common
Metabolism and nutrition disorders	Tumour lysis syndrome	Not known
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
	Myopathy/Muscular disorder[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 and squamous cell carcinoma of skin

[b] includes, but not limited to, angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, and urticaria

[c] includes facial nerve disorder, facial paralysis, facial paresis, Bell's palsy

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

[e] includes haemorrhage at various sites including, but not limited to, cerebral haemorrhage, intracranial haemorrhage, vaginal haemorrhage, heavy menstrual bleeding, intermenstrual bleeding, haematochezia, haemoptysis, haemothorax, gastrointestinal haemorrhage and haematuria
[f] includes, but not limited to, pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial, thrombosis, phlebitis, superior vena cava syndrome, mesenteric vein thrombosis and vena cava thrombosis
[g] includes colitis, colitis ulcerative, enterocolitis and proctitis
[h] includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, myositis
[i] includes, but not limited to, fluid retention, peripheral oedema, localised oedema, generalised oedema and swelling

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: anaemia, 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 Combo 450 ISP, RPED was reported in 22.3% (83/372) of patients. RPED was Grade 1 (asymptomatic) in 15.6% (58/372) of patients, Grade 2 in 5.1% (19/372) of patients and Grade 3 in 1.6 % (6/372) of patients. Most events were reported as retinopathy, retinal detachment, subretinal fluid, macular oedema, and central serous chorioretinopathy and led to dose interruptions or dose modifications in 3.8% (14/372) of patients. The median time to onset of the first event of RPED (all grades) was 1.4 month (range 0.0 to 17.5 months).
Visual impairment, including vision blurred and reduced visual acuity, occurred in 23.1% (86/372) 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 Combo 450 ISP, LVD was reported in 9.4 % (35/372) of patients. Grade 3 events occurred in 1.3 % (5/372) of patients. LVD led to treatment discontinuation in 0.8% (3/372) of patients and led to dose interruptions or dose reductions in 6.2 % (23/372) of patients.
The median time to first occurrence of LVD (any grade) was 5.2 months (range 0.0 to 25.7 months) in patients who developed an LVEF below 50 %. The mean LVEF value dropped by 5.3 % in the Combo 450 ISP, from a mean of 63.3 % at baseline to 58.0 %. LVD was generally reversible following dose reduction or dose interruption.

Haemorrhage
Haemorrhagic events were observed in 16.7% (62/372) of patients in the Combo 450 ISP. Most events were Grade 1 or 2:13.2% (49/372) and 3.5% (13/372) were Grade≥ 3. Few patients requiring dose interruptions or dose reductions (2.4% or 9/372). Haemorrhagic events led to discontinuation of treatment in 0.8 % (3/372) of patients. The most frequent haemorrhagic events were haematuria in 2.7 % (10/372) of patients, haematochezia in 2.7% (10/372) and rectal haemorrhage in 2.2% (8/372) of patients. Fatal gastric ulcer haemorrhage with multiple organ failure as a concurrent cause of death,

occurred in one patient. Cerebral haemorrhage/intracranial haemorrhage occurred in 1.6% (6/372) of patients with fatal outcome in 4 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 11.0 % (41/372) of patients treated with the Combo 450 ISP. Hypertension events were reported as Grade 3 in 5.1 % (19/372) of patients, including hypertensive crisis (0.3 % (1/372). Hypertension led to dose interruption or adjustment in 2.2 % (8/372) of patients. Hypertensive adverse reactions required additional therapy in 7.5 % (28/372) of patients.

Venous thromboembolism
In the Combo 450 ISP, VTE occurred in 4.8% (18/372) of patients, including 1.9% (7/372) of patients who developed pulmonary embolism. VTE was reported as Grade 1 or 2 in 4.0 % (15/372) of patients and Grade 3 or 4 in 0.8 % (3/372) of patients. VTE led to dose interruptions or dose modifications in 1.1% (4/372) patients and to additional therapy in 4.6% (17/372) 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 Combo 450 ISP, rash occurred in 20.4% (76/372) of patients. Most events were mild, with Grade 3 or 4 events reported in 1.1% (4/372) of patients. Rash led to treatment discontinuation in 0.8% (3/372) of patients and to dose interruption or dose modification in 2.4% (9/372) of patients.

Dermatitis acneiform
In the Combo 450 ISP, dermatitis acneiform occurred in 4.0% (15/372) of patients. Dermatitis acneiform was reported as Grade 1 or 2 in 3.8% (14/372) of patients and Grade 3 in 0.3% (1/372) of patients. No event led to treatment discontinuation. Dose modification was reported in 0.5 % (2/372) 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 Combo 450 ISP, photosensitivity was observed in 4.3% (16/372) of patients. Most events were Grade 1-2, with Grade 3 reported in 0.3% (1/372) of patients and no event led to discontinuation. Dose interruption or dose modification was reported in 0.3% (1/372) 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 Combo 450 ISP, mostly mild asymptomatic blood CK elevation was reported in 23.9% (89/372) of patients. The incidence of Grade 3 or 4 adverse reactions was 5.1 % (19/372). The median time to onset of the first event was 2.8 months (range: 0.5 to 26 months).

Rhabdomyolysis was reported in 0.3% (1/372) 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 Combo 450 ISP are listed below:

- Increased transaminases: 16.4% (61/372) overall – 6.5% (24/372) Grade 3
- Increased GGT: 11.3% (42/372) overall – 6.7% (25/372) Grade 3-4

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

Gastrointestinal disorders
In the Combo 450 ISP, diarrhoea was observed in 41.7% (155/372) of patients and was Grade 3 or 4 in 3.8% (14/372) of patients. Diarrhoea led to dose discontinuation in 0.8% of patients and to dose interruption or dose modification in 8.1 % of patients. Constipation occurred in 24.7% (92/372) of patients and was Grade 1 or 2. Abdominal pain was reported in 28.5% (106/372) of patients and was Grade 3 in 2.2 % (8/372) patients. Nausea occurred in 46.0% (171/372) with Grade 3 observed in 3.0% (11/372) of patients. Vomiting occurred in 31.2% (116/372) of patients with Grade 3 reported in 1.9% (7/372) 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 Combo 450 ISP, anaemia was reported in 23.1 % (86/372) of patients; 7.0% (26/372) of patients had Grade 3 or 4. No patients discontinued treatment due to anaemia, 3.2 % (12/372) 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 Combo 450 ISP, headache occurred in 18.8% (70/372) of patients including Grade 3 in 1.1% (4/372) 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 Combo 450 ISP, fatigue occurred in 48.1% (179/372) of patients including Grade 3 or 4 in 4.3% (16/372) 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 ISP (n = 372), 230 patients (61.8 %) were < 65 years old, 107 patients (28.8 %) were 65 -74 years old and 35 patients (9.4 %) were aged > 75. No overall differences in safety or efficacy were observed between elderly patients (≥ 65) and younger patients except diarrhoea and pruritus that were more frequently reported in elderly patients.
In the age subgroup of patients aged ≥ 75 years, Grade ≥3 adverse reactions (62.9% vs 47.5%), adverse reactions (all grades) requiring dose modification of any study drug (60.0% vs 48.1%) or leading to treatment discontinuation (25.7% vs 7.4%) were more frequently reported than in patients <75 years. The most common adverse reactions reported with a higher incidence in patients aged ≥ 75 years compared to patients aged < 75 years included fatigue, nausea, diarrhoea, vomiting and anaemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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, compared to treatment with either drug alone.

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 summarises 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 (%)	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) < 0.0001		
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; 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)

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.

Final efficacy analysis of Study CMEK162B2301, parts 1 and 2 (cut-off date: 31 March 2023)
The final efficacy analysis was consistent with the results of the interim analysis and showed a benefit in OS for Combo 450 over vemurafenib (HR 0.67 [95% CI:0.53,0.84] with median OS of 33.6 months *vs* 16.9 months). The PFS and ORR (per BIRC) results also confirmed a numerical benefit in favour of Combo 450, with a 7.6 months longer median PFS in the Combo 450 arm as compared to vemurafenib arm, see all detailed final efficacy results in Table 5 and Figures 1 and 2 below.

Moreover, Part 2 final analysis showed a numerical difference in OS for Combo 300 (Part 2) over Enco 300 monotherapy (Parts 1+2) (HR 0.89 [95%CI: 0.72,1.09] with median OS of 27.1 months [95% CI:21.6, 33.3] vs 22.7 months [95%CI:19.3,29.3]). The median PFS remained longer in the Combo 300 (Part 2) arm than in the Enco 300 (Parts 1+2) group with median PFS estimates of 12.9 months (95% CI: 10.9, 14.9) and 9.2 months (95% CI: 7.4, 11.1), respectively. The confirmed ORR (per BIRC) was 67.8% (95% CI: 61.8, 73.5) and 51.4% (95% CI 45.4, 57.4) in the Combo 300 (Part 2) and Enco 300 (Parts 1 + 2) arms, respectively. Similar results were observed per Investigator assessment.

Table 5: Study CMEK162B2301 : Final results on PFS, OS and confirmed ORR (cut-off date: 31 March 2023)

	Encorafenib + binimetinib N=192 (Combo 450)	**Encorafenib N=194 (Enco 300)**	**Vemurafenib N=191 (Vem)**
Final analysis, cut-off date: 31 March 2023			
PFS (per BIRC)			
Number of events (%)	123 (64.1)	119 (61.3)	121 (63.4)
Median[a], months (95% CI)	14.9 (11.0, 20.2)	9.6 (7.4, 14.8)	7.3 (5.6, 7.9)
HR[c] (95% CI) (vs Vem) Log-rank p-value (1-sided)*	0.51 (0.39, 0.66) <0.0001	0.68 (0.53, 0.88) 0.0017	
HR[c] (95% CI) (vs Enco 300) Log-rank p-value (1-sided)*	0.77 (0.60, 0.99) 0.0214		

OS			
Number of events (%)	139 (72.4)	125 (64.4)	147 (77.0)
Median [a], months (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Survival probability [b] at 1 year % (95%CI)	75.5 (68.8, 81.0)	74.6 (67.6, 80.3)	63.1 (55.7, 69.7)
at 2 years % (95% CI)	57.7 (50.3, 64.3)	49.1 (41.5, 56.2)	43.2 (35.9, 50.2)
at 3 years % (95% CI)	46.5 (39.3, 53.4)	40.9 (33.6, 48.1)	31.4 (24.8, 38.2)
at 5 years % (95% CI)	34.7 (28.0, 41.5)	34.9 (27.9, 42.0)	21.4 (15.7, 27.8)
at 9 years % (95% CI)	26.0 (19.8, 32.5)	27.8 (21.1, 34.8)	18.2 (12.8, 24.3)
HR[c] (95% CI) (vs Vem) Log-rank p-value (1-sided)*	0.67 (0.53, 0.84) 0.0003	0.74 (0.58, 0.94) 0.0063	
HR[c] (95% CI) (vs Enco 300) Log-rank p-value (1-sided)*	0.93 (0.73, 1.19) 0.2821		
Confirmed Best Overall Response (per BIRC)			
Confirmed ORR [d], n (%) (95% CI)	123 (64.1) (56.8, 70.8)	100 (51.5) (44.3, 58.8)	78 (40.8) (33.8, 48.2)
CR, n (%)	29 (15.1)	17 (8.8)	16 (8.4)
PR, n (%)	94 (49.0)	83 (42.8)	62 (32.5)
SD, n (%)	44 (22.9)	52 (26.8)	71 (37.2)
DCR [d], n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	155 (81.2) (74.8, 86.4)
Duration of Response (per BIRC)			
Median [a], months (95% CI)	18.6 (12.7, 27.6)	15.5 (11.1, 29.5)	12.3 (6.9, 14.5)

CI=Confidence Interval; CR=Complete Response; PR=Partial response; SD=stable disease; DCR=Disease Control Rate (CR+PR+SD+Non-CR/Non-PD); HR=hazard ratio; ORR=objective response rate (CR+PR); PR and CR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met.

[a] Median (time to event) and its 95% CIs are generated by KM estimation with Brookmeyer & Crowley method

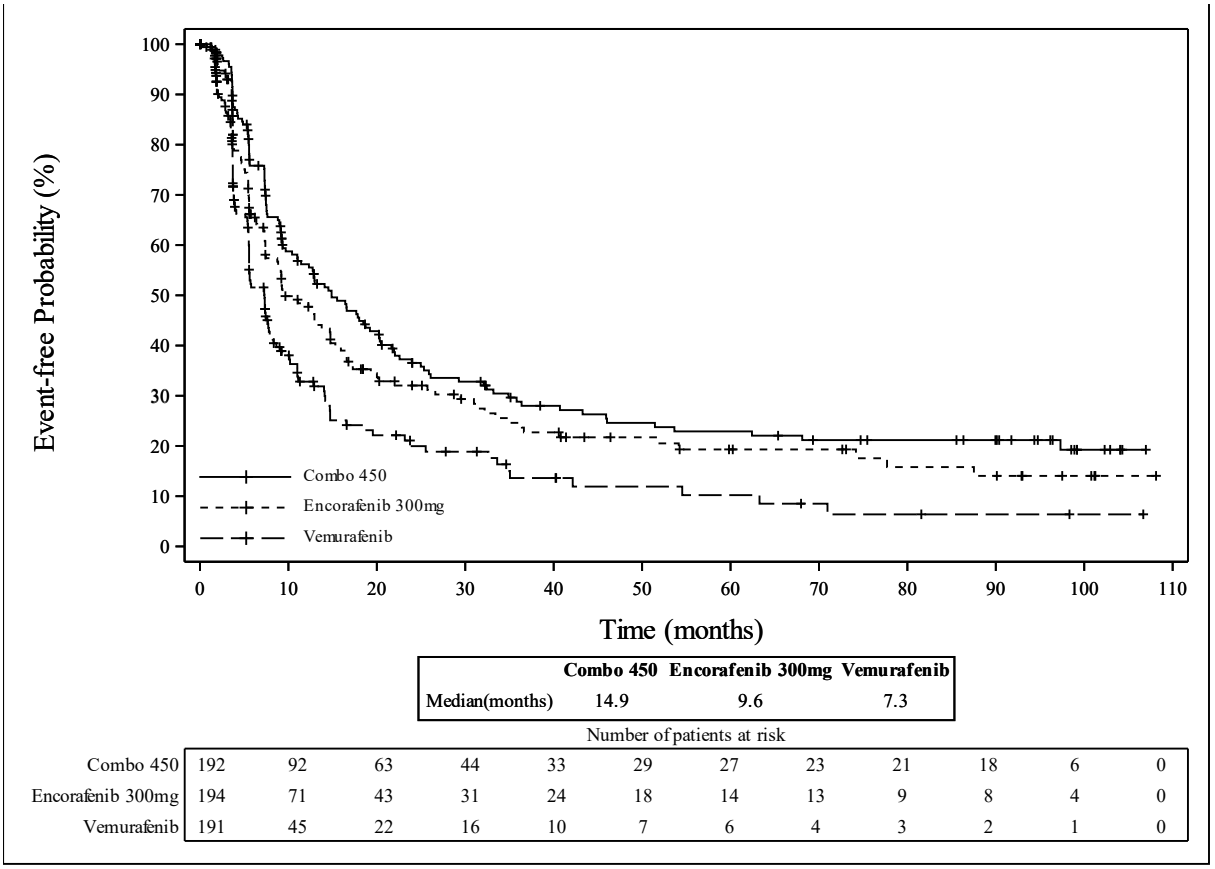
[b] Survival probability (obtained from the KM survival estimates, Greenwood formula used for CIs)

[c] Both Log-rank test and Cox PH model are stratified by IVRS AJCC stage and ECOG Performance status

[d] estimated 95% CI are obtained using the exact Clopper-Pearson method

*nominal p-value

Figure 1 Study CMEK162B2301: Kaplan-Meier plot of PFS by BIRC (cut-off date: 31 March 2023)

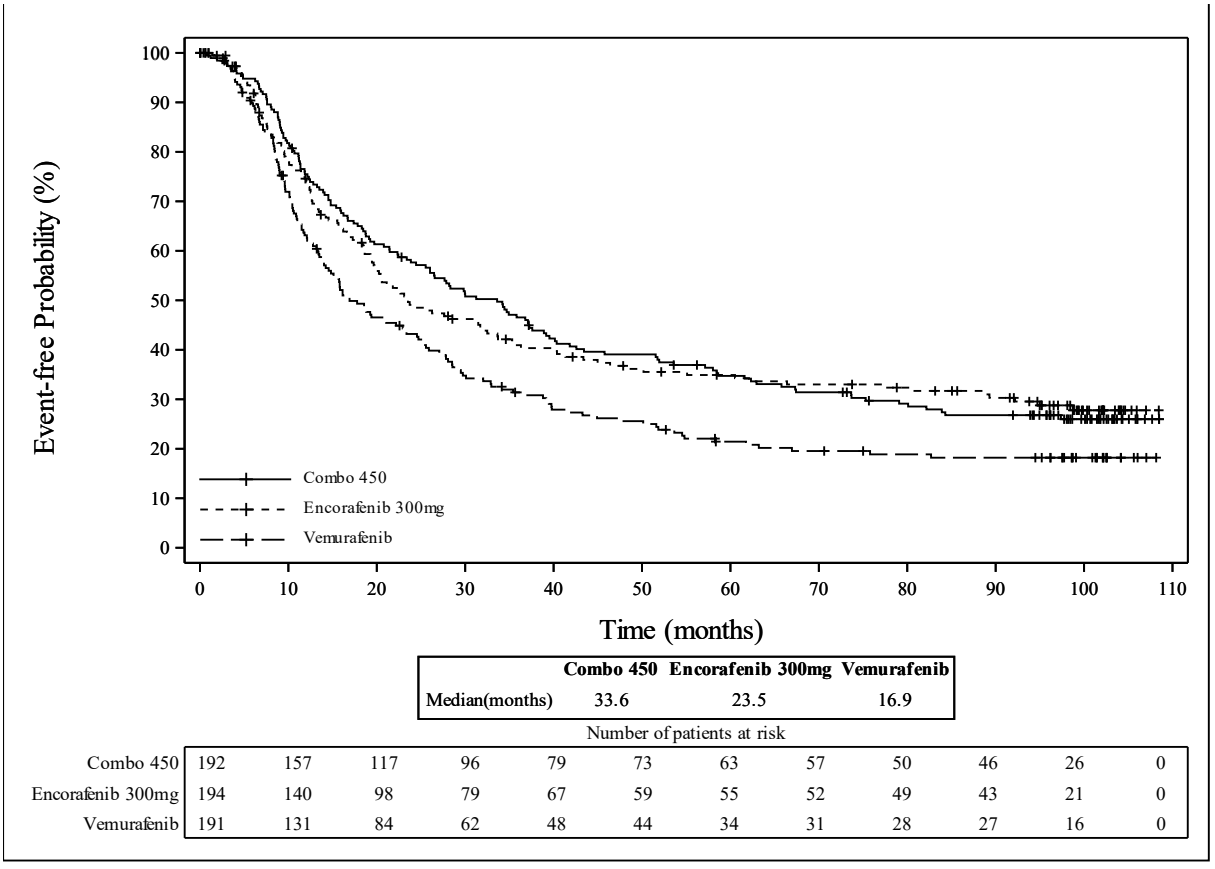


	Combo 450	Encorafenib 300mg	Vemurafenib
Median(months)	14.9	9.6	7.3

Number of patients at risk

Combo 450	192	92	63	44	33	29	27	23	21	18	6	0
Encorafenib 300mg	194	71	43	31	24	18	14	13	9	8	4	0
Vemurafenib	191	45	22	16	10	7	6	4	3	2	1	0

Figure 2 Study CMEK162B2301: Kaplan-Meier plot of OS (cut-off date: 31 March 2023)



	Combo 450	Encorafenib 300mg	Vemurafenib
Median(months)	33.6	23.5	16.9

Number of patients at risk

Combo 450	192	157	117	96	79	73	63	57	50	46	26	0
Encorafenib 300mg	194	140	98	79	67	59	55	52	49	43	21	0
Vemurafenib	191	131	84	62	48	44	34	31	28	27	16	0

BRAF V600E Mutant advanced Non-small cell lung cancer – Study ARRAY-818-202

The safety and efficacy of binimetinib in combination with encorafenib were studied in a Phase II, open-label, multicentre, non-comparative study (Study ARRAY-818-202, PHAROS). Patients were required to have histologically-confirmed metastatic NSCLC with a BRAF V600E mutation, ECOG performance status of 0 or 1, and measurable disease. Patients had received 0 or 1 prior line of systemic therapy in the metastatic setting. Prior use of BRAF inhibitors or MEK inhibitors was prohibited.

Patients were enrolled based on the determination of a BRAF V600E mutation in tumour tissue or blood (e.g., ctDNA genetic testing) by a local laboratory assay. Central confirmation of the BRAF V600E mutation status (i.e. any short variant with protein effect V600E) was performed on archival or fresh tumour tissue collected at enrolment and utilized the FoundationOne CDx – F1CDx (tissue) assay.

The analytical sensitivity was assessed through the Limit of Detection (LoD) study for F1CDx using the hit rate method (defined as the lowest level with ≥ 95% detection) by evaluating variant allele frequency (VAF) for short variants. For F1CDx, the median LoD for substitution was determined to be 3.2% VAF.

A total of 98 patients were enrolled and treated with binimetinib 45 mg orally twice daily and encorafenib 450 mg orally once daily. Treatment continued until disease progression or unacceptable toxicity.

The primary efficacy outcome measure was objective response rate (ORR) and was according to RECIST v1.1 as evaluated by an Independent Radiology Review (IRR). Secondary endpoints included duration of response (DoR), disease control rate (DCR), PFS and OS. Results of the primary analysis with 18.2 months for treatment naïve and 12.8 months previously treated patients are presented below.

Of the 98 patients enrolled in this study, 59 (60.2%) were treatment naïve. The median age of patients was 70 years (47-86), 53% were female, 88% were white and 30% had never smoked. 74% had a baseline ECOG performance status of 1 (67.8 % of participants had a baseline PS 1 in the treatment naïve population and 82.1% in the previously treated population). All patients had metastatic disease of which 8% had brain metastases at baseline and 97% had adenocarcinoma.

At the time of the primary analysis, the median duration of exposure was 15.1 months in treatment naïve patients and 5.4 months in previously treated patients. In the overall population, the median relative dose intensity (RDI) was 95.4% for binimetinib and 99.2% for encorafenib.

At the time of the primary analysis, the primary endpoint of IRR-assessed ORR in the treatment naïve population was 74.6% (95% CI: 61.6, 85.0), including 9 (15.3%) CRs and 35 (59.3%) PRs.
The ORR by IRR in the previously treated population was 46.2% (95% CI: 30.1, 62.8), including 4 (10.3%) CRs and 14 (35.9%) PRs.

Results updated with an additional 10-month follow-up (median duration of exposure of 16.3 months in treatment naïve patients and 5.5 months in previously treated patients) are provided in Table 6.

Table 6: Study ARRAY-818-202: Efficacy Results

	Binimetinib with Encorafenib	
	Treatment Naïve (N=59)	**Previously Treated (N=39)**
ORR per IRR		
ORR, % (95% CI)	75% (62, 85)	46% (30, 63)
CR, %	15%	10%
PR, %	59%	36%
DoR per IRR	N=44	N=18
Median DoR, months (95% CI)	40.0 (23.1, NE)*	16.7 (7.4, NE)*
% with DoR ≥12 months	64%	44%

* Results from a sensitivity analysis considering new anti-cancer therapy as an event in addition to progression and death are 23.1 months in treatment naïve patients (14.8; NE) and 12.0 months (6.3; NE) in previously treated patients.
N = number of patients; ORR = Objective Response Rate; CI = Confidence Interval; CR = Complete Response; PR = Partial Response; DoR = Duration of Response; IRR= Independent Radiology Review; NE = not estimable

Cardiac electrophysiology
In the safety analysis of pooled studies, the incidence of new QTcF prolongation > 500 ms was 1.1 % (4/363) in the Combo 450 ISP (n = 372), and 2.5 % (5/203) in the encorafenib single agent group of patients with melanoma. QTcF prolongation of > 60 ms compared to pre-treatment values was observed in 6.0 % (22/364) patients in the Combo 450 ISP, 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 waived the obligation to submit the results of studies with binimetinib in all subsets of the paediatric population in lung cancer (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. 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 %) Cmax,ss was 654 ng/mL (34.7 %) and mean AUCss was 2.35 ug.h/mL (28.0 %) in combination with encorafenib as estimated by population PK modelling in patients with unresectable or metastatic BRAF V600 mutant melanoma. 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 in adults.

No clinical data are available in the paediatric population. The safety profile in the paediatric population is unknown. In adolescents with BRAF V600-mutant metastatic melanoma aged 12 to <18 years, population pharmacokinetic simulations show that the following doses and dose reductions for the management of adverse reactions result in plasma exposure similar to that achieved in adults:

- Weighing 40 kg and more: the adult dose 45 mg BID with the same dose reduction: 30 mg BID.
- Weighing less than 40 kg: 30 mg BID, based on the simulations at lower doses, no dose reduction is proposed,

Children under 12 years should not be treated with 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 $\leq$ 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
Mektovi 15 mg film-coated tablets
Poly(vinyl alcohol) (E1203)
Macrogol 3350 (E1521)
Titanium dioxide (E171)
Talc (E533b)
Iron oxide yellow (E172)
Iron oxide black (E172)

Mektovi 45 mg film-coated tablets
Poly(vinyl alcohol) (E1203)
Macrogol 4000 (E1521)
Calcium carbonate (E170)
Talc (E533b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Mektovi 15 mg film-coated tablets
PVC/PVDC/Alu blister containing 12 tablets. Each pack contains either 84 or 168 tablets**.**
Not all pack sizes may be marketed.

Mektovi 45 mg film-coated tablets
PVC/PVDC/Alu blister containing 14 tablets. Each pack contains either 28 or 56 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

8. MARKETING AUTHORISATION NUMBER(S)

Mektovi 15 mg film-coated tablets

EU/1/18/1315/001 84 film-coated tablets
EU/1/18/1315/002 168 film-coated tablets

Mektovi 45 mg film-coated tablets

EU/1/18/1315/003 28 film-coated tablets
EU/1/18/1315/004 56 film-coated tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018
Date of latest renewal: 23 June 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

PIERRE FABRE MEDICAMENT PRODUCTION
Site Progipharm, rue du Lycée
45500 GIEN
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mektovi 15 mg film-coated tablets
binimetinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 15 mg binimetinib.

3. LIST OF EXCIPIENTS

The tablets also contain lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 film-coated tablets
168 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1315/001 84 film-coated tablets
EU/1/18/1315/002 168 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mektovi 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SNNN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Mektovi 15 mg tablets
binimetinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pierre Fabre Médicament

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mektovi 45 mg film-coated tablets
binimetinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 45 mg binimetinib.

3. LIST OF EXCIPIENTS

The tablets also contain lactose. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1315/003 28 film-coated tablets
EU/1/18/1315/004 56 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

mektovi 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Mektovi 45 mg tablets
binimetinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pierre Fabre Médicament

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Mektovi 15 mg film-coated tablets
Mektovi 45 mg film-coated tablets
binimetinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mektovi is and what it is used for

Mektovi is an anti-cancer medicine that contains the active substance binimetinib. It is used in adults in combination with another medicine containing encorafenib to treat a type of skin cancer called melanoma or a type of lung cancer called non-small cell lung cancer (NSCLC), when the cancer has
- a particular change (mutation) in a gene responsible for producing a protein called BRAF, and
- spread to other parts of the body or cannot be removed by surgery.

Mutations in the BRAF gene can produce proteins that cause your cancer to grow. Mektovi targets another protein called “MEK” that stimulates cancer cell growth. When Mektovi is used in combination with encorafenib (which targets the changed “BRAF” protein), the combination slows down or stops the growth of your cancer.

2. What you need to know before you take Mektovi

Before starting treatment your doctor will check for BRAF mutation.

As Mektovi is to be used in combination with encorafenib, read the encorafenib leaflet carefully as well as this leaflet.

Do not take Mektovi
- if you are allergic to binimetinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Mektovi about all of your medical conditions, particularly if you have any of the following:
- heart problems
- bleeding problems or if you are taking medicines that may cause bleeding

- eye problems including glaucoma or increased pressure in your eyes
- muscle problems
- high blood pressure
- blood clots
- lung or breathing problems
- liver problems

Tell your doctor if you have ever had blockage in the vein carrying blood away from the eye (retinal vein occlusion), as Mektovi is not recommended in such cases.

Tell your doctor if you have had a different type of cancer than melanoma or NSCLC, as binimetinib when taken with encorafenib may worsen certain other types of cancers.

Tell your doctor, pharmacist or nurse immediately if you get the following while you are taking this medicine:

- Heart problems: Mektovi can make your heart work less well, or make existing heart problems worse. Your doctor will check that your heart is working properly before and during your treatment with this medicine. Talk to your doctor immediately if you have any symptoms of heart problems such as feeling dizzy, tired, lightheaded, if you have shortness of breath, if you feel like your heart is pounding, racing, beating irregularly or if you have swelling in the legs.

- Bleeding problems: Mektovi may cause serious bleeding problems. Talk to your doctor immediately if you have any symptoms of bleeding problems such as coughing up of blood, blood clots, vomit containing blood or that looks like “coffee grounds”, red or black stools that look like tar, passing blood in the urine, stomach (abdominal) pain, unusual vaginal bleeding. Also tell your doctor if you have headache, dizziness or weakness.

- Eye problems: Mektovi can cause serious eye problems. Talk to your doctor immediately if you get blurred vision, loss of vision or other vision changes (such as coloured dots in your vision), halo (seeing blurred outline around objects). Your doctor will examine your eyes for any problems with your sight while you are taking Mektovi.

- Muscle problems: Mektovi can cause breakdown of muscle (rhabdomyolysis). Your doctor will run blood tests to check for muscle problems before and during treatment. As a precaution, drink plenty of fluids during treatment. Talk to your doctor immediately if you get muscle pain, cramps, stiffness, spasm, dark urine.

- High blood pressure: Mektovi can raise blood pressure. Your doctor or nurse will check your blood pressure before and during treatment with Mektovi. Talk to your doctor immediately if you get severe headache, feel dizzy, lightheaded or if your blood pressure measured on a home blood pressure device is much higher than usual.

- Blood clots: Mektovi can cause blood clots in your arms or legs, and if a clot travels to your lungs it could lead to death. Talk to your doctor immediately if you get chest pain, sudden shortness of breath, trouble breathing, pain in your legs with or without swelling, swelling in your arms and legs, or a cool, pale arm or leg. If necessary, your doctor may interrupt your treatment or stop it altogether.

- Lung or breathing problems: This medicine 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 your treatment or stop it altogether.

- Skin changes: Mektovi, when taken with encorafenib, may cause other types of skin cancer such as cutaneous squamous cell carcinoma. Your doctor will check your skin before initiation

of treatment, every 2 months during treatment, and for up to 6 months after you stop taking these medicines to look for any new skin cancer. Tell your doctor immediately if you detect any skin changes during and after the treatment including: new wart, skin sore or reddish bump that bleeds or does not heal, or a change in size or colour of a mole.
Additionally, your doctor needs to check for squamous cell carcinoma on your head, neck, mouth and lymph glands, and you will have CT scans regularly. This is a precaution in case a squamous cell carcinoma develops inside your body. Genital examinations (for women) and anal examinations are also recommended before the initiation and at the end of your treatment.

- Liver problems: Mektovi can cause abnormal blood tests related to your liver (raised levels of liver enzymes). Your doctor will run blood tests to check your liver before and during treatment.

If you experience the following symptoms, contact your doctor immediately as this can be a life-threatening condition: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These may be caused by a group of metabolic complications that can occur during treatment of cancer that are caused by the breakdown products of dying cancer cells (Tumour lysis syndrome (TLS)) and can lead to changes in kidney function (see also section 4: Possible side effects).

Children and adolescents
Mektovi is not recommended for children and adolescents under 18 years of age. This medicine has not been studied in this age group.

Other medicines and Mektovi
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
Some medicines may affect how Mektovi works or make it more likely that you will have side effects. In particular, tell your doctor if you are taking anything in this list or any other medicines:

- some medicines to treat bacterial infections such as rifampicin, ciprofloxacin
- some medicines typically used to treat epilepsy such as phenobarbital, phenytoin, carbamazepine
- some medicines to treat HIV such as indinavir, atazanavir
- a medicine for carcinoma treatment called sorafenib
- an herbal treatment for depression: St. John’s wort
- medicine used to treat depression such as duloxetine
- medicine typically used to treat high cholesterol such as pravastatin
- a medicine used to treat breathing problems, theophylline.

Pregnancy
Mektovi is not recommended during pregnancy. It may cause permanent harm or birth defects to an unborn baby.
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
If you are a woman who could become pregnant, you must use reliable contraception while you are taking Mektovi, and you must continue to use reliable contraception at least 1 month after taking your last dose. Contact your doctor straightaway if you become pregnant while taking Mektovi.

Breast-feeding
Mektovi is not recommended while breast-feeding. It is not known if Mektovi passes into breast milk. If you are breast-feeding, or planning to breast-feed, ask your doctor for advice before taking this medicine.

Driving and using machines
Mektovi can affect your ability to drive or use machines. Avoid driving or using machines if you have any problems with your vision or have any other side effects that can affect your ability to drive or use machines (see section 4), while taking Mektovi. Talk to your doctor if you are not sure you can drive.

Mektovi contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to take Mektovi

How much to take
Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Mektovi is 45 mg (three 15 mg tablets or one 45 mg tablet) twice daily, approximately 12 hours apart**,** corresponding to a total daily dose of 90 mg. You will also receive treatment with another medicine, encorafenib.

If you get serious side effects (such as heart, eye or skin problems) your doctor may lower the dose or stop treatment temporarily or permanently.

How to take Mektovi
Swallow the tablets whole with water. Mektovi can be taken with food or between meals.

If you cannot swallow the tablets whole, you may disperse Mektovi 15 mg tablets in a small glass (approximately 10 mL, roughly 2 teaspoons) of either water, orange juice or apple juice and taken immediately. The glass should be rinsed with a further 10 mL (roughly 2 teaspoons) of water, orange juice or apple juice, and content drunk immediately. If not used within 30 minutes, discard the mixture and prepare a new one.

If you are sick
If you vomit at any time after taking Mektovi, do not take an additional dose. Take the next dose as scheduled.

If you take more Mektovi than you should
If you take more tablets than you should, contact your doctor, pharmacist or nurse straightaway. If possible, show them this leaflet and the medicine package.

If you forget to take Mektovi
If you miss a dose of Mektovi, take it as soon as you remember. However, if the missed dose is more than 6 hours late, skip that dose and take your next dose at the usual time. Then continue taking your tablets at regular times as usual.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Mektovi
It is important to take Mektovi for as long as your doctor prescribes it. Do not stop taking this medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Mektovi may cause serious side effects. Tell your doctor immediately if you have any of the following serious side effects, either for the first time or if they get worse (see also section 2).

Heart problems: Mektovi can affect how well your heart works (left ventricular ejection fraction decrease); 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

High blood pressure: Mektovi can increase blood pressure. Tell your doctor immediately if you get severe headache, feel dizzy or lightheaded or if your blood pressure measured on a home blood pressure device is much higher than usual.

Blood clots: 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 problems: Mektovi can cause fluid to leak under the retina in the eye, leading to detachment of different layers in the eye (retinal pigment epithelial detachment) which could lead to:
- blurred vision, loss of vision, or other vision changes (such as coloured dots in your vision)
- halo (seeing blurred outline around objects)
- eye pain, swelling or redness

Muscle problems: Mektovi can cause 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 problems: Mektovi can cause serious bleeding problems. Tell your doctor right away 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 stools that look like tar
- passing blood in the urine
- stomach (abdominal) pain
- unusual vaginal bleeding

Other skin cancers: When Mektovi is taken with encorafenib, the patient may develop different types of skin cancer such as cutaneous squamous cell carcinoma. Usually, these skin cancers (see also section 2) are confined to a small area and can be removed with surgery and treatment with Mektovi (and encorafenib) can continue without interruption.

Tumour lysis syndrome: Mektovi can cause a rapid breakdown of cancer cells which in some people may be fatal. Symptoms may include nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness.

Other side effects when Mektovi and encorafenib are taken together
Besides the serious side effects mentioned above, people taking Mektovi and encorafenib together may also get the following side effects.

Very common (may affect more than 1 in 10 people)
- reduced red blood cell count (anaemia)
- problem with the nerves resulting in pain, loss of sensation or tingling in hands and feet
- headache
- dizziness
- bleeding at various sites in the body
- problems with your vision (visual impairment)
- stomach pain
- diarrhoea
- being sick (vomiting)
- feeling sick (nausea)
- constipation
- itching
- dry skin
- hair loss or thinning (alopecia)
- skin rash of various types
- thickening of the outer layers of the skin
- joint pain (arthralgia)
- muscle disorders
- back pain
- pain in the extremities
- fever
- swelling of the hands or feet (peripheral oedema), localised swelling
- fatigue
- abnormal blood test results for liver function
- abnormal blood test result related to blood creatine kinase, indicating damage to heart and muscle

Common (may affect up to 1 in 10 people)
- some types of skin tumours such as skin papilloma
- allergic reaction that may include swelling of the face and difficulty breathing
- changes in the way things taste
- inflammation of the eye (uveitis)
- inflammation of the colon (colitis)
- redness, chapping or cracking of the skin
- inflammation of the fatty layer under the skin, symptoms include tender skin nodules
- skin rash with a flat discoloured area or raised bumps like acne (dermatitis acneiform)
- redness, skin peeling or blisters on hand and feet (palmar plantar erythrodysesthesia or hand and foot syndrome)
- 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)
- increased skin sensitivity to sunlight

Uncommon (may affect up to 1 in 100 people)
- some types of skin tumours such as basal cell carcinoma
- weakness and paralysis of face muscles
- inflammation of the pancreas (pancreatitis) causing severe abdominal pain

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mektovi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mektovi contains

- The active substance is binimetinib.
  Mektovi 15 mg film-coated tablet: each film-coated tablet contains 15 mg of binimetinib.
  Mektovi 45 mg film-coated tablet: each film-coated tablet contains 45 mg of binimetinib.
- The other ingredients are:
  - Tablet core: lactose monohydrate, cellulose microcrystalline (E460i), silica colloidal anhydrous (E551), croscarmellose sodium (E468) and magnesium stearate (E470b). See section 2 “Mektovi contains lactose”.
  - Tablet film-coat:

  Mektovi 15 mg film-coated tablet: poly(vinyl alcohol) (E1203), macrogol 3350 (E1521), titanium dioxide (E171), talc (E533b), iron oxide yellow (E172) and iron oxide black (E172).
  Mektovi 45 mg film-coated tablet: poly(vinyl alcohol) (E1203), macrogol 4000 (E1521), calcium carbonate (E170), talc (E533b).

What Mektovi looks like and contents of the pack

Mektovi 15 mg film-coated tablets
The film-coated tablets are yellow/dark yellow, unscored biconvex, oval film-coated tablets debossed with “A” on one side and “15” on the other side.
Mektovi 15 mg film-coated tablets is available in packs of 84 tablets (7 blisters of 12 tablets each) or 168 tablets (14 blisters of 12 tablets each).
Not all pack sizes may be marketed.

Mektovi 45 mg film-coated tablets
The film-coated tablets are white to off-white, unscored biconvex, ovaloid film-coated tablets debossed with “45” on one side.
Mektovi 45 mg film-coated tablets is available in packs of 28 tablets (2 blisters of 14 tablets each) or 56 tablets (4 blisters of 14 tablets each).
Not all pack sizes may be marketed.

Marketing Authorisation Holder

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur

France

Manufacturer
PIERRE FABRE MEDICAMENT PRODUCTION
Site Progipharm, Rue du Lycée
45500 GIEN
France

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.