ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Braftovi 50 mg hard capsules
Braftovi 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Braftovi 50 mg hard capsules
Each hard capsule contains 50 mg of encorafenib.

Braftovi 75 mg hard capsules
Each hard capsule contains 75 mg of encorafenib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Braftovi 50 mg hard capsules
Orange opaque cap and flesh opaque body, printed with a stylised “A” on the cap and “LGX 50mg” on the body. The length of the capsule is approximately 22 mm.

Braftovi 75 mg hard capsules
Flesh coloured opaque cap and white opaque body, printed with a stylised “A” on the cap and “LGX 75mg” on the body. The length of the capsule is approximately 23 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib.

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

Dose reduction recommendations for encorafenib are presented in Table 1.

Table 1: Recommended dose modifications for encorafenib (when used in combination with binimetinib)

Dose level	**Encorafenib dose** when used in combination with binimetinib
Starting dose	450 mg once daily
1st dose reduction	300 mg once daily
2nd dose reduction	200 mg once daily
Subsequent modification	There are limited data for dose reduction to 100mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100mg once daily.

Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced at 300 mg once daily during the time of binimetinib dose interruption (see section 4.2 of binimetinib Summary of Product Characteristics [SmPC]) 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 Table 2), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued.

For information on the posology and recommended dose modifications of binimetinib, see section 4.2 of binimetinib SmPC.

Dose modifications in case of adverse reactions are provided below and in Table 2.

For new primary cutaneous malignancies: No dose modifications are required for encorafenib.

For new primary non-cutaneous RAS mutation-positive malignancies: it should be considered to discontinue encorafenib and binimetinib permanently.

If treatment-related toxicities occur, then encorafenib and binimetinib should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for binimetinib only (adverse reactions primarily related to binimetinib) are: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation and rhabdomyolysis, and venous thromboembolism (VTE).
If one of these toxicities occurs, see section 4.2 of binimetinib SmPC for dose modification instructions for binimetinib.

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

Severity of adverse reaction[a]	**Encorafenib**
Cutaneous reactions	
• Grade 2	Encorafenib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, encorafenib should be withheld until Grade 0 or 1 and then resumed at the same dose.
• Grade 3	Encorafenib 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	Encorafenib should be permanently discontinued.

Severity of adverse reaction[a]	**Encorafenib**
Palmar-plantar erythrodysaesthesia syndrome (PPES)	
• Grade 2	Encorafenib should be maintained and supportive measures such as topical therapy should be instituted. If not improved despite supportive therapy within 2 weeks, encorafenib should be withheld until improved to Grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.
• Grade 3	Encorafenib should be withheld, supportive measures such as topical therapy should be instituted, and the patient should be reassessed weekly. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to Grade 0 or 1.
Uveitis including iritis and iridocyclitis	
• Grade 1-3	If Grade 1 or 2 uveitis does not respond to specific (e.g. topical) ocular therapy or for Grade 3 uveitis, encorafenib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. If uveitis is Grade 1 and it improves to Grade 0, then treatment should be resumed at the same dose. If uveitis is Grade 2 or 3 and it improves to Grade 0 or 1, then treatment should be resumed at a reduced dose. If not improved within 6 weeks, ophthalmic monitoring should be repeated and encorafenib should be permanently discontinued.
• Grade 4	Encorafenib should be permanently discontinued and a follow up with ophthalmologic monitoring should be performed.
QTc Prolongation	
• QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Encorafenib should be withheld (see monitoring in section 4.4). Encorafenib should be resumed at a reduced dose when QTcF ≤500 ms. Encorafenib should be discontinued if more than one recurrence.
• QTcF>500 ms and increased by >60 ms from pre-treatment values	Encorafenib should be permanently discontinued (see monitoring in section 4.4).
Liver laboratory abnormalities	
• Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x ≤5x upper limit of normal (ULN))	Encorafenib should be maintained. If no improvement within 4 weeks, encorafenib should be withheld until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resumed at the same dose.
• First occurrence of Grade 3 (AST or ALT >5x ULN and blood bilirubin >2x ULN)	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, it should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued

Severity of adverse reaction[a]	Encorafenib
• First occurrence of Grade 4 (AST or ALT >20 ULN)	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue encorafenib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Encorafenib should be permanently discontinued.

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

Table 3: Recommended dose modifications for encorafenib (used in combination with binimetinib) for other adverse reactions

Severity of adverse reaction	Encorafenib
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, It should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of any Grade 4 adverse reaction	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 adverse reactions	Permanent discontinuation of encorafenib should be considered.
• Recurrent Grade 4 adverse reactions	Encorafenib 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 encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose.

Vomiting
In case of vomiting after administration of encorafenib, the patient should not take an additional 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
Patients with mild to severe hepatic impairment may have increased encorafenib exposure (see section 5.2).
Administration of encorafenib should be undertaken with caution at a reduced dose of 300 mg once daily in patients with mild hepatic impairment (Child-Pugh Class A).
No dosing recommendation can be made in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment based on a population pharmacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential need for dose adjustment cannot be determined. Encorafenib should be used with caution in patients with severe renal impairment (see sections 4.4 and 5.2).

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

Method of administration

Braftovi is for oral use. The capsules are to be swallowed whole with water. They may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided (see sections 4.4 and 4.5)

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

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

BRAF mutation testing
Before taking encorafenib in combination with binimetinib, patients must have BRAF V600 mutation confirmed by a validated test. The efficacy and safety of encorafenib have been established only in patients with tumours expressing BRAF V600E and V600K mutations. Encorafenib should not be used in patients with wild type BRAF malignant melanoma.

Encorafenib in combination with binimetinib in patients who have progressed on a BRAF inhibitor
There are limited data for the use of the combination of encorafenib with binimetinib 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.

Encorafenib in combination with binimetinib in patients with brain metastases
There are limited efficacy data with the combination of encorafenib and binimetinib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain (see section 5.1).

Left ventricular dysfunction (LVD)
LVD defined as symptomatic or asymptomatic decreases in ejection fraction has been reported when encorafenib is used in combination with binimetinib.
It is recommended that left ventricular ejection fraction (LVEF) is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of encorafenib and binimetinib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. If during treatment LVD occurs, see section 4.2 of binimetinib SmPC.

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

Haemorrhage
Haemorrhages, including major haemorrhagic events, can occur with encorafenib (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 or treatment discontinuation (see Table 3 in section 4.2) and as clinically indicated.

Ocular toxicities
Ocular toxicities including uveitis, iritis and iridocyclitis can occur when encorafenib is administered. RPED has also been reported in patients treated with encorafenib in combination with binimetinib (see section 4.8).
Patients should be assessed at each visit for symptoms of new or worsening visual disturbance. 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.
If, uveitis including iridocyclitis and iritis occurs during treatment, see section 4.2.
If during treatment patient develops RPED or RVO, see section 4.2 of binimetinib SmPC for guidance.

QT prolongation
QT Prolongation has been observed in patients treated with BRAF-inhibitors. A thorough QT study to evaluate the QT prolongation potential of encorafenib has not been conducted.
Overall, results suggest that single agent encorafenib has the potential to cause mild increases in heart rate. Across pooled combination studies of encorafenib and binimetinib at the recommended doses and a single-agent encorafenib study, results suggest that encorafenib has the potential to result in small increases in QTc interval (see section 5.1).
There are insufficient data to exclude a clinically significant exposure dependent QT prolongation.
Due to the potential risk for QT prolongation, it is recommended that serum electrolytes abnormalities, including magnesium and potassium, are corrected and risk factors for QT prolongation controlled (e.g. congestive heart failure, bradyarrhythmias) before treatment initiation and during treatment.
It is recommended that an electrocardiogram (ECG) is assessed before initiation of encorafenib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. The occurrence of QTc prolongation can be managed with dose reduction, interruption or discontinuation with correction of abnormal electrolytes and control of risk factors (see section 4.2).

New primary malignancies
New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when encorafenib is administered (see section 4.8).

Cutaneous malignancies
Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma has been observed in patients treated with BRAF-inhibitors including encorafenib. New primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib (see section 4.8).
Dermatologic evaluations should be performed prior to initiation of therapy with encorafenib in combination with binimetinib, every 2 months while on therapy and for up to 6 months following discontinuation of the combination. Suspicious skin lesions should be managed with dermatological excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Encorafenib and binimetinib should be continued without any dose modification.

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 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. It should be considered to permanently discontinue encorafenib in patients who develop RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

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

Hepatic impairment
As encorafenib is primarily metabolised and eliminated via the liver, patients with mild to severe hepatic impairment may have increased encorafenib exposure over the range of inter-subject variability exposure (see section 5.2).
In the absence of clinical data, encorafenib is not recommended in patients with moderate or severe hepatic impairment.
Administration of encorafenib should be undertaken with caution at a reduced dose in patients with mild hepatic impairment (see section 4.2).
Closer monitoring of encorafenib related toxicities in patients with mild hepatic impairment is recommended, including clinical examination and liver function tests, with assessment of ECGs as clinically appropriate during treatment.

Renal impairment
There are no data available in patients with severe renal impairment (see sections 4.2 and 5.2). Encorafenib should be used with caution in patients with severe renal impairment. Creatinine elevation has been commonly reported with encorafenib as single agent or in combination with binimetinib. Observed cases of renal failure including acute kidney injury and renal impairment were generally associated with vomiting and dehydration. Other contributing factors included diabetes and hypertension. Blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation (see Table 3 in section 4.2). Patients should ensure adequate fluid intake during treatment.

Effects of other medicinal products on encorafenib.
Concurrent use of strong CYP3A inhibitors during treatment with encorafenib should be avoided. If concomitant use with a strong CYP3A inhibitor is necessary, patients should be carefully monitored for safety (see section 4.5).
Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on encorafenib
Encorafenib is primarily metabolised by CYP3A4.

CYP3A4 inhibitors
Co-administration of moderate (diltiazem) and strong (posaconazole) CYP3A4 inhibitors with single doses of encorafenib in healthy volunteers resulted in a 2 and 3-fold increase in the area under the concentration-time curve (AUC), respectively and in 44.6% and 68.3% increase in maximum encorafenib concentration (C_{max}) respectively.
Model based predictions indicate that the effect of posaconazole after repeated administrations could be similar for AUC (3-fold increase) and slightly greater for C_{max} (2.7-fold increase). Model-based predictions for ketoconazole suggest an increase of approx. 5-fold for encorafenib AUC and 3 to 4--fold for encorafenib C_{max}.

Therefore, concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity, see section 5.2). Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice. If concomitant use of a strong CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety.
Moderate CYP3A4 inhibitors should be co-administered with caution. Examples of moderate CYP3A4 inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, diltiazem, amprenavir and imatinib. When encorafenib is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.

CYP3A4 inducers
Co-administration of encorafenib with a CYP3A4 inducer was not assessed in a clinical study; however, a reduction in encorafenib exposure is likely and may result in compromised efficacy. Examples of moderate or strong CYP3A4 inducers include, but are not limited to carbamazepine, rifampicin, phenytoin and St. John's Wort. Alternative agents with no or minimal CYP3A induction potential should be considered.

Effects of encorafenib on other medicinal products
CYP substrates
Encorafenib is both an inhibitor and inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g., hormonal contraceptives) may result in increased toxicity or loss of efficacy of these agents. Agents that are CYP3A4 substrates should be co-administered with caution.
Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 (e.g. raltegravir, atorvastatin, dolutegravir) may have increased exposure and should be therefore administered with caution.

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

Transporter substrates
Encorafenib potentially inhibits a number of transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 (such as furosemide, penicillin) or agents that are substrates of the hepatic transporters OATP1B1, OATP1B3, OCT1 (such as atorvastatin, bosentan) or substrates of BCRP (such as methotrexate, rosuvastatin) or substrates of P-gp (e.g. posaconazole) may have increased exposure and should be therefore co-administered with caution.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females
Women of childbearing potential must use effective contraception during treatment with encorafenib and for at least 1 month following the last dose. Encorafenib may decrease the efficacy of hormonal contraceptives (see section 4.5). Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment with encorafenib and for at least 1 month following the last dose.

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

Breast-feeding
It is unknown whether encorafenib or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding

or to discontinue encorafenib 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 effects of encorafenib on fertility in humans. Based on findings in animals, the use of encorafenib may impact fertility in males of reproductive potential (see section 5.3). As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis.

4.7 Effects on ability to drive and use machines

Encorafenib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with encorafenib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions 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 encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the pooled Combo 450 population), based on two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, Part 1).
At the recommended dose (n = 274) in patients with unresectable or metastatic melanoma, the most common adverse reactions (≥25%) occurring in patients treated with encorafenib administered with binimetinib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, arthralgia, blood CK increased and myalgia.

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

The encorafenib single agent (300 mg orally once daily) safety profile is based on data from 217 patients with unresectable or metastatic BRAF V600-mutant melanoma (hereafter referred to as the pooled encorafenib 300 population). The most common adverse drug reactions (ADRs) (≥25%) reported with encorafenib 300 were hyperkeratosis, alopecia, PPES, fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus.

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), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse reactions

Frequency	Encorafenib single agent 300 mg (n = 217)	Encorafenib 450 mg in combination with binimetinib (n = 274)
Neoplasms benign, malignant and unspecified		
Very common	Skin papilloma[*] Melanocytic nevus	
Common	cuSCC[a] New Primary Melanoma[*]	cuSCC[a] Basal cell carcinoma[*] Skin papilloma[*]
Uncommon	Basal cell carcinoma	
Blood and lymphatic system disorders		
Very common		Anaemia
Immune system disorders		
Common	Hypersensitivity[b]	Hypersensitivity[b]
Metabolism and nutrition disorders		
Very common	Decreased appetite	
Psychiatric disorders		
Very common	Insomnia	
Nervous system disorders		
Very common	Headache[*] Neuropathy peripheral[*] Dysgeusia[*]	Neuropathy peripheral[*] Dizziness[*] Headache[*]
Common	Facial paresis[c]	Dysgeusia[*]
Uncommon		Facial paresis[c]
Eye disorders		
Very common		Visual impairment[*] RPED [*]
Common		Uveitis [*]
Uncommon	Uveitis[*]	
Cardiac disorders		
Common	Supraventricular tachycardia[d]	LVD[h]
Vascular disorders		
Very common		Haemorrhage[i] Hypertension [*]
Common		VTE[j]
Gastrointestinal disorders		
Very common	Nausea Vomiting[*] Constipation	Nausea Vomiting[*] Constipation Abdominal pain[*] Diarrhoea[*]
Common		Colitis [k]
Uncommon	Pancreatitis[*]	Pancreatitis[*]

Skin and subcutaneous tissue disorders		
Very common	PPES Hyperkeratosis* Rash* Dry skin* Pruritus* Alopecia* Erythema [e] Skin hyperpigmentation*	Hyperkeratosis* Rash* Dry skin* Pruritus* Alopecia*
Common	Dermatitis acneiform* Skin exfoliation[f] Photosensitivity*	Dermatitis acneiform* PPES Erythema* Panniculitis* Photosensitivity*
Musculoskeletal and connective tissue disorders		
Very common	Arthralgia* Myalgia[g] Pain in extremity Back pain	Arthralgia* Muscular disorders/Myalgia[l] Pain in extremity Back pain
Common	Arthritis *	
Uncommon		Rhabdomyolysis
Renal and urinary disorders		
Common	Renal failure *	Renal failure *
General disorders and administration site conditions		
Very common	Fatigue * Pyrexia*	Fatigue* Pyrexia* Peripheral oedema[m]
Investigations		
Very common	Gamma-glutamyl transferase (GGT) increased*	Blood creatine phosphokinase increased Gamma-glutamyl transferase (GGT) increased* Transaminase increased*
Common	Transaminase increased* Blood creatinine increased* Lipase increased	Blood alkaline phosphatase increased Blood creatinine increased* Amylase increased Lipase increased
Uncommon	Amylase increased	

*composite terms which included more than one preferred term

[a] includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma and squamous cell carcinoma of skin

[b] includes angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis and urticaria

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

[d] includes extrasystoles, sinus tachycardia, supraventricular extrasystoles, tachyarrhythmia, tachycardia

[e] includes erythema, generalised erythema, plantar erythema

[f] includes dermatitis exfoliative, skin exfoliation, exfoliative rash

[g] includes myalgia, muscle fatigue, muscle injury, muscle spasm, muscle weakness

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

[i] includes haemorrhage at various sites including cerebral haemorrhage

[j] includes pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial and thrombosis

[k] includes colitis, colitis ulcerative, enterocolitis and proctitis

[l] includes myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, myositis

[m] includes fluid retention, peripheral oedema, localised oedema

When encorafenib was used at a dose of 300 mg once daily in combination with binimetinib 45 mg twice daily (Combo 300) in study CMEK162B2301-Part 2, the frequency category was lower compared to the pooled Combo 450 population for the following adverse reactions: anemia, peripheral neuropathy, haemorrhage, hypertension, pruritus (common); and colitis, increased amylase and increased lipase (uncommon).

Description of selected adverse reactions

Cutaneous malignancies
Cutaneous squamous cell carcinoma
In the pooled Combo 450 population, cuSCC including keratoacanthomas was observed in 3.3% (9/274) of patients. The median time to onset of the first event of cuSCC (all grades) was 6.5 months (range 1.0 to 22.8 months).

In the pooled encorafenib 300 population, cuSCC was reported in 7.4% (16/217) patients. For patients in the Phase III study (CMEK162B2301) who developed cuSCC, the median time to onset of the first event of cuSCC (all grades) was 2.3 months (range 0.3 to 12.0 months).

New primary melanoma
In the pooled encorafenib 300 population, new primary melanoma events occurred in 4.1% of patients (9 /217) and was reported as Grade 1 in 1.4% (3/217) of patients, Grade 2 in 2.1% (4/217) of patients, Grade 3 in 0.5% (1/217) of patients and Grade 4 in 0.5% (1/217) of patients.

Ocular events
In the pooled Combo 450 population, uveitis was reported in 4.4% (12/274) of patients, and was Grade 1 in 0.4% (1/274), Grade 2 in 3.6% (10/274) and Grade 3 in 0.4% (1/274). Visual impairment, including blurred vision and reduced visual acuity, occurred in 21.5% (59/274) of patients. Uveitis and visual impairment were generally reversible.
RPED occurred in 29.6% (81/274) of patients, most of them had Grade 1-2 and 1.8% (5/274) had Grade 3 events.

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
LVD was reported when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

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

In Study CMEK162B2301-Part 2, in the Combo 300 arm, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3-4 in 1.6% (4/257) of patients.

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

Venous thromboembolism
VTE was reported when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

Pancreatitis
Pancreatic enzyme elevation, mostly asymptomatic, was reported in the pooled Combo 450 population. Amylase and lipase elevations were reported in 3.3% (9/274) and 5.1% (14/274) of patients, respectively. Pancreatitis was reported in 0.7% (2/274) of patients. Both patients experienced Grade 3 events. Pancreatitis led to dose interruption or adjustment in (0.4 %) 1/274 of patients.

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

In the pooled encorafenib 300 population, rash was reported in 43.3% (94/217) of patients. Most events were mild, with Grade 3 or 4 events reported in 4.6% (10/217) of patients. Rash led to discontinuation in 0.5% (1/217) of patients and to dose interruption or dose modification in 7.4% (16/217) of patients.

Palmar-plantar erythrodysaesthesia syndrome (PPES)
PPES was reported in 6.2% (17/274) of patients in the pooled Combo 450 population. All the PPES adverse reactions were either Grade 1 (3.3%) or Grade 2 (2.9%). Dose interruption or dose modification occurred in 1.1% (3/274) of patients.

In the Combo 300 arm in Part 2 of the pivotal study, PPES was observed in 3.9% (10/257) of patients with Grade 3 reported in 0.4% (1/257) of patients.

In the pooled encorafenib 300 population, PPES was reported in 51.6% (112/217) of patients. Most events were mild-moderate: Grade 1 in 12.4% (27/217) of patients, Grade 2 in 26.7% (58/217) and Grade 3 in 12.4% (27/217) of patients. PPES led to discontinuation in 4.1% (9/217) of patients and to dose interruption or dose modification in 23.0% (50/217) of patients.

Dermatitis acneiform
Dermatitis acneiform was reported when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

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

In the pooled encorafenib 300 population, photosensitivity was reported in 4.1% (9/217) of patients. All events were Grade 1-2. No event required discontinuation, dose modification or interruption.

Facial paresis
In the pooled Combo 450 population, facial paresis occurred in 0.7% (2/274) of patients including Grade 3 in 0.4% (1/274) of patients. The events were reversible, and no event led to treatment discontinuation. Dose interruption or modification was reported in 0.4% (1/274) of patients.

In the pooled encorafenib 300 population, facial paresis was observed in 7.4% (16/217) of patients. Most events were mild-moderate: Grade 1 in 2.3% (5/217); Grade 2 in 3.7% (8/217) and Grade 3 in 1.4% (3/217) of patients. The median time to onset of the first event of facial paresis was 0.3 months (range 0.1 to 12.1 months). Facial paresis was generally reversible and led to treatment discontinuation

in 0.9% (2/217). Dose interruption or modification was reported in 3.7% (8/217) and symptomatic treatment including corticosteroids was reported in 5.1% (11/217) of patients.

CK elevation and rhabdomyolysis
CK elevation and rhabdomyolysis occurred when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

Renal dysfunction
In the pooled Combo 450 population, mild, mostly Grade 1, asymptomatic blood creatinine elevation was noted in 6.2% (17/274) of patients treated with the Combo 450 mg. The incidence of Grade 3 or 4 elevation was 0.7% (2/274). Renal failure events, including acute kidney injury and renal impairment, were reported in 3.3% (9/274) patients treated with encorafenib and binimetinib with Grade 3 or 4 events in 2.2% (6/274) of patients. Renal failure was generally reversible with dose interruption, rehydration and other general supportive measures.

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

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

In Study CMEK162B2301-Part 2, in the Combo 300 arm, the incidence of liver laboratory abnormalities was:

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

Gastrointestinal disorders
In the pooled Combo 450 population, diarrhoea was observed in 38% (104/274) of patients and was Grade 3-4 in 3.3% (9/274) patients. Diarrhoea led to dose discontinuation in 0.4% of patients and to dose interruption or dose modification in 4.4% of patients.
Constipation occurred in 24.1% (66/274) of patients and was Grade 1 or 2. Abdominal pain was reported in 27.4% (75/274) of patients and was Grade 3 in 2.6% (7/274) patients. Nausea occurred in 41.6% (114/274) with Grade 3 or 4 observed in 2.6% (7/274) of patients. Vomiting occurred in 28.1% (77/274) of patients with Grade 3 or 4 reported in 2.2% (6/274) of patients.

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

Gastrointestinal disorders were typically managed with standard therapy.

Anaemia
In the pooled Combo 450 population, anaemia was reported in 19.7% (54/274) of patients; 4.7% (13/274) patients had a Grade 3 or 4. No patients discontinued treatment due to anaemia, 1.5% (4/274) required dose interruption or dose modification.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, anaemia was observed in 9.7% (25/257) of patients with Grade 3-4 reported in 2.7% (7/257) patients.

Headache
In the pooled Combo 450 population, headache occurred in 21.5% (59/274) of patients, including Grade 3 in 1.5% (4/274) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, headache was reported in 12.1% (31/257) of patients and was Grade 3 in 0.4% (1/257) of patients.

Fatigue
In the pooled Combo 450 population, fatigue occurred in 43.8% (120/274) of patients including Grade 3 in 2.9% (8/274) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3-4 events.

Special populations

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

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

Symptoms
At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (Grade 3 hypercreatinaemia) was observed in 3 out of 14 patients. The highest administered dose occurred as a dosing error in one patient who took encorafenib at a dose of 600 mg twice daily for 1 day (total dose 1200 mg). Adverse reactions reported by this patient were Grade 1 events of nausea, vomiting and blurred vision; all subsequently resolved.

Management
There is no specific treatment for overdose.
Since encorafenib is moderately bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with encorafenib. There is no known antidote for encorafenib. In the event of an overdose, encorafenib treatment should be interrupted and renal function must be monitored as well as adverse reactions. Symptomatic treatment and supportive care should be provided as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor, ATC code: L01XE46

Mechanism of action

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor. The half maximal inhibitory concentration (IC_{50}) of encorafenib against $BRAF^{V600E}$, BRAF and CRAF enzymes was determined to be 0.35, 0.47 and 0.30 nM, respectively. The encorafenib dissociation half-life was >30 hours and resulted in prolonged pERK inhibition. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). Specifically, encorafenib inhibits *in vitro* and *in vivo* $BRAF^{V600E, D and K}$ mutant melanoma

cell growth. Encorafenib does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF.

Combination with binimetinib
Encorafenib and binimetinib (a MEK inhibitor, see section 5.1 of binimetinib SmPC) both inhibit the MAPK pathway, resulting in higher anti-tumour activity.
Additionally, the combination of encorafenib and binimetinib prevented the emergence of resistance in $BRAF^{V600E}$ mutant human melanoma xenografts *in vivo*.

Clinical efficacy and safety

BRAF V600 Mutant Unresectable or Metastatic Melanoma
The safety and efficacy of encorafenib in combination with binimetinib were evaluated in a 2-part Phase III, randomised (1:1:1) active-controlled, open-label, multicentre 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 encorafenib 450 mg orally daily and binimetinib 45 mg orally twice daily (Combo 450, n = 192), encorafenib 300 mg orally daily (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 Enco 300 and 6.2 months in patients treated with vemurafenib. The median relative dose intensity (RDI) for Combo 450 was 100% for encorafenib and 99.6% for binimetinib; 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 5 and Figure 1 summarize 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 5: Study CMEK162B2301, Part 1: Progression-free survival and confirmed overall response results (independent central review)

	Encorafenib + binimetinib N=192 (Combo 450)	**Encorafenib N=194 (Enco300)**	**Vemurafenib N=191 (Vem)**
Cut-off date: 19 May 2016			
PFS (primary analysis)			
Number of events (progressive disease (PD)) (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	7.3 (5.6, 8.2)
HR[a] (95% CI) (vs Vem) p-value (stratified log-rank)[b]	0.54 (0.41, 0.71) <0.001		
HR[a] (95% CI) (vs Vem) Nominal p-value		0.68 (0.52, 0.90) 0.007	
HR[a] (95% CI) (vs Enco 300) p-value (stratified log-rank)[b]	0.75 (0.56,1.00) 0.051		
Confirmed overall responses			
Overall response rate, n (%) (95% CI)	121 (63.0) (55.8, 69.9)	98 (50.5) (43.3, 57.8)	77 (40.3) (33.3, 47.6)
CR, n (%)	15 (7.8)	10 (5.2)	11 (5.8)
PR, n (%)	106 (55.2)	88 (45.4)	66 (34.6)
SD, n (%)	46 (24.0)	53 (27.3)	73 (38.2)
DCR, n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	156 (81.7) (75.4, 86.9)
Duration of response			
Median, months (95% CI)	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)
Updated analysis, cut-off date: 07 November 2017			
PFS			
Number of events (progressive disease) (%)	113 (58.9)	112 (57.7)	118 (61.8)
Median, months (95% CI)	14.9 (11.0, 20.2)	9.6 (7.4,14.8)	7.3 (5.6, 7.9)
HR[a] (95% CI) (vs Vem) Nominal p-value	0.51 (0.39, 0.67) <0.001		
HR[a] (95% CI) (vs Vem) Nominal p-value		0.68 (0.52, 0.88) 0.0038	

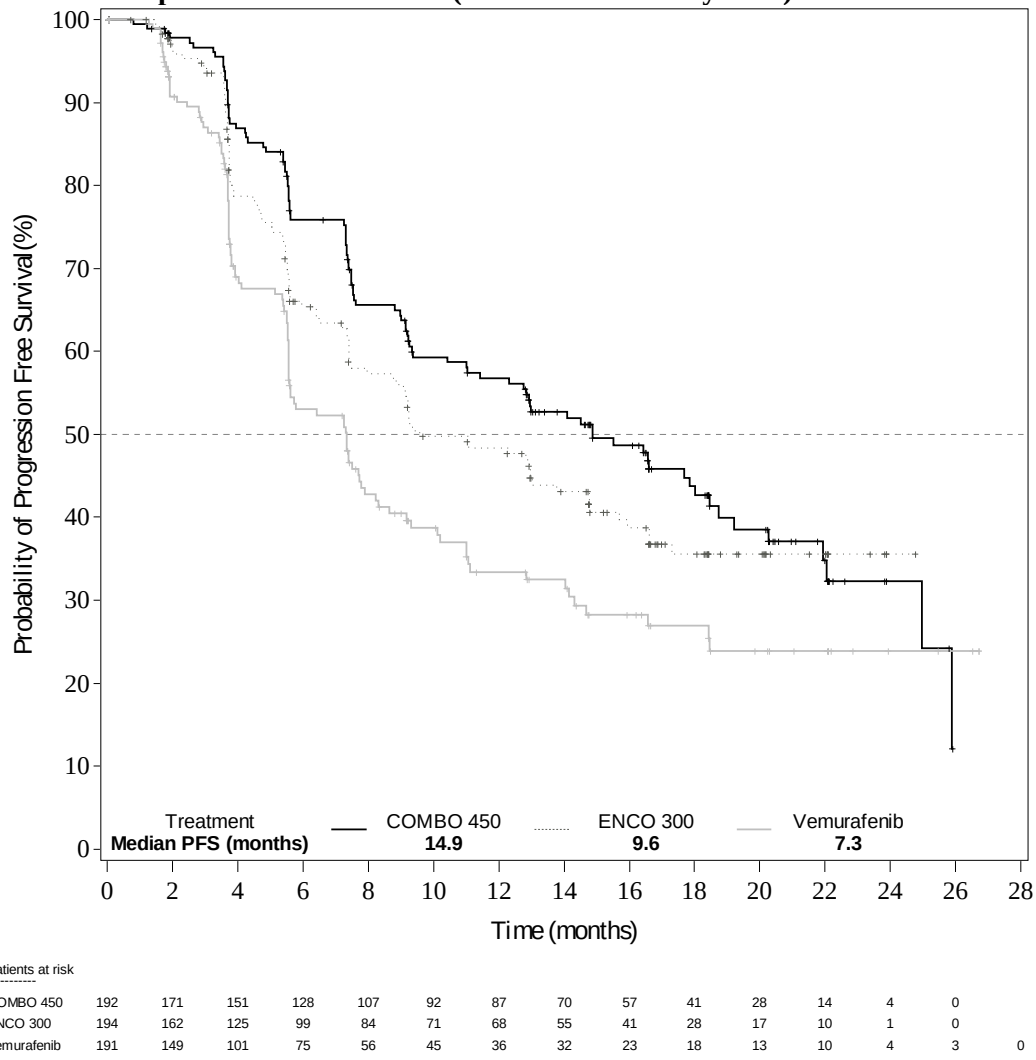
HR[a] (95% CI) (vs Enco 300) Nominal p-value	0.77 (0.59,1.00) 0.0498		

CI=Confidence interval; CR=Complete Response; DCR=Disease Control Rate (CR+PR+SD+Non-CR/Non-PD; Non-CR/Non-PD applies only to patients without a target lesion who did not achieve CR or have PD); HR=hazard ratio; NE=Not estimable; PFS=progression-free survival; PR=Partial response; SD=stable disease. Vem=vemurafenib.

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

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

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



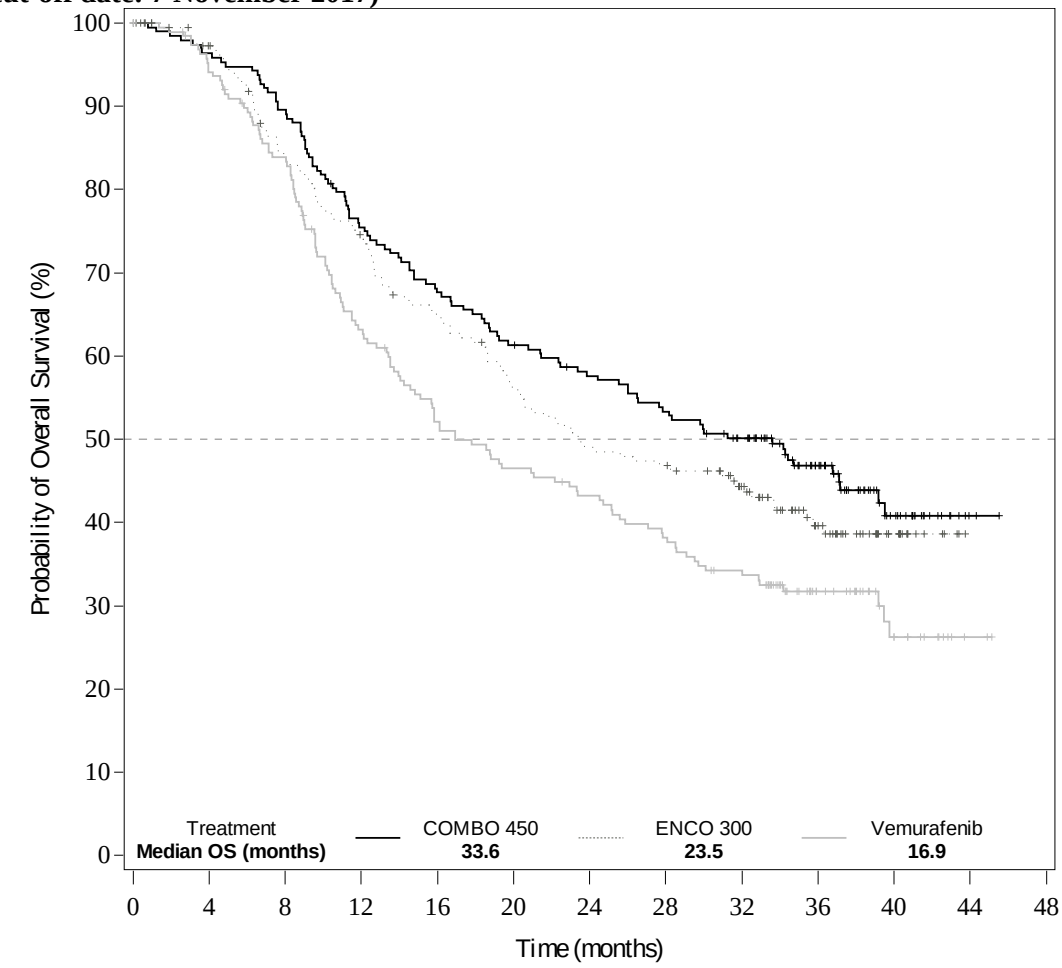
An interim OS analysis of Study CMEK162B2301 Part 1, (cut-off date 07 November 2017) demonstrated a statistically significant improvement in OS for Combo 450 compared with vemurafenib (see Table 6 and Figure 2).

A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4% Combo 450 arm, 36.1% encorafenib arm, 39.8% vemurafenib arm).

Table 6: Study CMEK162B2301, Part 1: Overall survival interim results (cut-off date: 7 November 2017)

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

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



Patients at risk

COMBO 450	192	185	172	144	129	117	108	100	89	57	23	2	0
ENCO 300	194	178	151	133	115	98	86	82	67	40	16	0	
Vemurafenib	191	176	155	115	94	84	77	68	59	30	14	2	0

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 reactions. A definitive 10% deterioration in FACT-M and in EORTC QLQ-C30 was significantly delayed in patients treated with Combo 450 relative to other treatments. The median time to definitive 10% deterioration in the FACT-M score was not reached in the Combo 450 arm and was 22.1 months (95% CI: 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI: 0.29, 0.72). An analysis of time to definitive 10% deterioration in EORTC QLQ-C30 score provided with similar results.
Patients receiving Combo 450 reported no change or a slight improvement in the mean change from baseline EQ-5D-5L index score at all visits, whilst patients receiving vemurafenib or encorafenib reported decreases at all visits (with statistical significant differences). An evaluation of change over time in score yielded the same trend for EORTC QLQ-C30 and at all visit for FACT-M.

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

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

Cardiac Electrophysiology
In the safety analysis of pooled studies, the incidence of new QTc prolongation >500 ms was 0.7% (2/268) in the encorafenib 450 mg plus binimetinib group, and 2.5% (5/203) in the encorafenib single agent group. QTc prolongation of >60 ms compared to pre-treatment values was observed in 4.9% (13/268) patients in the encorafenib plus binimetinib group, and in 3.4% (7/204) in the encorafenib single agent group (see Sections 4.2 and 4.4).

Paediatric population

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

5.2 Pharmacokinetic properties

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumours, including advanced and unresectable or metastatic cutaneous melanoma harbouring a BRAF-V600E or K mutation. The pharmacokinetics of encorafenib have been shown to be approximatively dose linear after single and multiples doses. After repeat once-daily dosing, steady-state conditions were reached within 15 days. The accumulation ratio of approximately 0.5 is likely due to auto-induction of CYP3A4. The inter-subject variability (CV%) of AUC is ranged from 12.3% to 68.9%.

Absorption

After oral administration, encorafenib is rapidly absorbed with a median T_{max} of 1.5 to 2 hours. Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, at least 86% of the encorafenib dose was absorbed. Administration of a single 100 mg dose of encorafenib with a high-fat, high-calorie meal decreased the C_{max} by 36%, while the AUC was unchanged. A drug interaction study in healthy subjects indicated the extent of encorafenib exposure was not altered in the presence of a gastric pH-altering agent (rabeprazole).

Distribution

Encorafenib is moderately (86.1%) bound to human plasma proteins *in vitro*. Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, the mean (SD) blood-to-plasma concentration ratio is 0.58 (0.02) and the mean (CV%) apparent volume of distribution (Vz/F) of encorafenib is 226 L (32.7%).

Biotransformation

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, metabolism was found to be the major clearance pathway for encorafenib (approximately 88% of the recovered radioactive dose). The predominant biotransformation reaction of encorafenib was N-dealkylation. Other major metabolic pathways involved hydroxylation, carbamate hydrolysis, indirect glucuronidation and glucose conjugate formation.

Elimination

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, radioactivity was eliminated equally in both the faeces and urine (mean of 47.2%). In urine, 1.8% of the radioactivity was excreted as encorafenib. The mean (CV%) apparent clearance (CL/F) of encorafenib was 27.9 L/h (9.15%). The median (range) encorafenib terminal half-life ($T_{1/2}$) was 6.32 h (3.74 to 8.09 h).

Medicinal product interactions

Effect of CYP enzymes on encorafenib
Encorafenib is metabolised by CYP3A4, CYP2C19 and CYP2D6. *In vitro*, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively).

Effect of encorafenib on CYP substrates
In vitro experiments indicate encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9 and CYP3A4/5, as well as a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Simulations of 450 mg encorafenib co-administered with probe substrates for CYP2B6, CYP1A2, CYP2C9, CYP2C19 and CYP2D6 on Day 1 and Day 15 all indicated no clinically relevant interactions are expected. For co-administration with CYP3A4 and UGT1A1 substrates that undergo gut extraction, a minor to moderate interaction is expected. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction and therefore no DDI with encorafenib is expected. Additionally, no differences in exposure have been observed clinically when binimetinib is co-administered with encorafenib.

Effect of transporters on encorafenib
Encorafenib was found to be a substrate of the P-glycoprotein (P-gp) transporters. Inhibition of P-gp is unlikely to result in a clinically important increase in encorafenib concentrations as encorafenib exhibits high intrinsic permeability. The involvement of several uptake transporter families (OCT1, OATP1B1, OATP1B3 and OATPB1) was investigated *in vitro* using relevant transporter inhibitors. The data suggest that hepatic uptake transporters are not involved in encorafenib distribution into primary human hepatocytes.

Effect of encorafenib on transporters
In vitro, encorafenib inhibited the hepatic transporter OCT1, but is unlikely to be an effective inhibitor clinically. Based on *in vitro* studies, there is potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 and hepatic transporters OATP1B1 and OATP1B3 at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut and BCRP at the expected clinical concentrations.

Special populations

Age
Based on a population pharmacokinetic analysis, age was found to be a significant covariate on encorafenib volume of distribution, but with high variability. Given the small magnitude of these changes and high variability, these are unlikely to be clinically meaningful, and no dose adjustments are needed for elderly patients.

Gender
Based on a population pharmacokinetic analysis gender was not found to be a significant model covariate on clearance or volume of distribution. As a result, no major changes in encorafenib exposure are expected based upon gender.

Body weight
Based on a population pharmacokinetic analysis, body weight was found to be a significant model covariate on clearance and volume of distribution. However, given the small magnitude of change in clearance and the high variability in the predicted volume of distribution in the model, weight is unlikely to have a clinically relevant influence on the exposition of encorafenib.

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

Hepatic impairment
Results from a dedicated clinical study indicate a 25% higher total encorafenib exposures in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55% increase of the unbound encorafenib exposure.
The pharmacokinetics of encorafenib has not been evaluated clinically in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolised and eliminated via the liver, based on PBPK modelling, patients with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4).

Renal impairment
Encorafenib undergoes minimal renal elimination. No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of encorafenib.
In a population pharmacokinetic analysis, no clear trend in encorafenib CL/F was observed in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) or moderate (eGFR 30 to 59 mL/min/1.73 m^2) renal impairment compared with subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2). A small decrease in CL/F (≤5%) was predicted for patients with mild and moderate renal impairment, which is unlikely to be clinically relevant. The pharmacokinetics of encorafenib have not been studied in patients with severe renal impairment.

5.3 Preclinical safety data

In the 4-week and 13-week rat toxicity studies, clinical signs, reduced body weight reduced epididymides and prostate weights and microscopic findings in testes, epididymides, stomach and skin were noted. Partial reversibility of these findings was noted after a 4-week recovery period. Additionally, in the 13-week rat toxicity study, reversible clinical pathology changes were noted at

doses ≥ 100 mg/kg/d. No NOAEL could be established for the 4-week study. The NOAEL for the 13-week study was at 14- to 32-times human therapeutic exposures.

In the 4-week and 13-week monkey toxicity study, isolated/sporadic episodes of emesis and diarrhoea as well as ophthalmic lesions were observed at slightly above human therapeutic exposures. Ophthalmic lesions were partially reversible and consisted of a separation or detachment in the retina between the outer rods and cones layer and retinal pigmented epithelium at the central macula at the fovea. This observation was similar to that described in humans as central serous-like chorioretinopathy or central serous retinopathy.

Encorafenib was not genotoxic.
Fertility studies were not conducted with encorafenib. In the sub-acute 28-day and sub-chronic 13-week rat toxicology studies, encorafenib treatment at 20 mg/kg/d (dose level approximately 8 times the human exposure at the recommended dose) resulted in decreased testes and epididymis weights with tubular degeneration and oligospermia. In the 13-week study, partial reversibility was noted at the highest dose level (60 mg/kg/d).

The embryo-foetal development study in rats indicated that encorafenib induced foetal toxicity with lower foetal weights and delays in skeletal development.
The embryo-foetal development study in rabbits indicated that encorafenib induced foetal toxicity with lower foetal weights and transitory changes in skeletal development. Dilatation of the aortic arc was observed in some foetuses.

Encorafenib was phototoxic in an *in vitro* 3T3 Neutral Red Uptake Test. Encorafenib was not a sensitiser in the *in vivo* mouse sensitization assay. Collectively, these data indicate that encorafenib has a risk of phototoxic potential and minimal risk for sensitization at therapeutic doses in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Copovidone (E1208)
Poloxamer 188
Cellulose microcrystalline (E460i)
Succinic acid (E363)
Crospovidone (E1202)
Silica colloidal anhydrous (E551)
Magnesium stearate (E470b)

Capsule shell

Gelatin (E441)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

Printing ink

Shellac (E904)
Iron oxide black (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Braftovi 50 mg hard capsules
Polyamide/aluminum/PVC/aluminum blister containing 4 capsules.
Each pack contains either 28 or 112 hard capsules.
Not all pack sizes may be marketed.

Braftovi 75 mg hard capsules
Polyamide/aluminum/PVC/aluminum blister containing 6 capsules.
Each pack contains either 42 or 168 hard capsules.
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 Médicament
45, place Abel Gance
92100 Boulogne-Billancourt
France

8. MARKETING AUTHORISATION NUMBER(S)

Braftovi 50 mg hard capsules

EU/1/18/1314/001 28 hard capsules
EU/1/18/1314/003 112 hard capsules

Braftovi 75 mg hard capsules

EU/1/18/1314/002 42 hard capsules
EU/1/18/1314/004 168 hard capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pierre Fabre Médicament Production
Aquitaine Pharm International 1
Avenue du Béarn
64320 Idron
France

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

Braftovi 50 mg hard capsules
encorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg encorafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
112 hard capsules

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

Store below 30°C. Store in the original package in order to protect from moisture.

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 Médicament
45, place Abel Gance
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1314/001 28 hard capsules
EU/1/18/1314/003 112 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

braftovi 50 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

Braftovi 50 mg capsules
encorafenib

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

Braftovi 75 mg hard capsules
encorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 75 mg encorafenib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

42 hard capsules
168 hard capsules

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

Store below 30°C. Store in the original package in order to protect from moisture.

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 Médicament
45, place Abel Gance
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1314/002 42 hard capsules
EU/1/18/1314/004 168 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

braftovi 75 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

Braftovi 75 mg capsules
encorafenib

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

Braftovi 50 mg hard capsules
Braftovi 75 mg hard capsules
encorafenib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 Braftovi is and what it is used for

Braftovi is an anti-cancer medicine that contains the active substance encorafenib. It is used in adults in combination with another medicine containing binimetinib to treat a type of skin cancer called melanoma when it 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 the melanoma to grow. Braftovi targets proteins made from this changed BRAF gene. When Braftovi is used in combination with binimetinib, which targets another protein that stimulates cancer cell growth, the combination slows down or stops the growth of your cancer.

2. What you need to know before you take Braftovi

Before starting treatment your doctor will check for the BRAF mutation.

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

Do not take Braftovi
- if you are allergic to encorafenib 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 Braftovi, about all of your medical conditions, particularly if you have any of the following:
- heart problems including alteration of the electrical activity of your heart (QT interval prolongation)
- bleeding problems or if you are taking medicines that may cause bleeding
- eye problems
- liver or kidney problems

Tell your doctor if you have had a different type of cancer than melanoma, as Braftovi 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: Braftovi when taken with binimetinib can make your heart work less well, alter the electrical activity of your heart called "QT interval prolongation" or make existing heart problems worse. Your doctor will check that your heart is working properly before and during your treatment with these medicines. 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: Braftovi 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: Braftovi, when taken with binimetinib, can cause serious eye problems. Talk to your doctor immediately if you get blurred vision, loss of vision, or other vision changes (e.g. 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 Braftovi.

- Skin changes: Braftovi may cause other types of skin cancer such as cutaneous squamous cell carcinoma. New melanomas may also occur while taking Braftovi. Your doctor will check your skin for any new skin cancers before treatment, every 2 months during treatment, and for up to 6 months after you stop taking Braftovi. Tell your doctor immediately if you detect skin changes during and after 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 and at the end of your treatment.

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

- Kidney problems: Braftovi can alter your kidney activity (often abnormal blood tests, more rarely dehydration and vomiting). Your doctor will run blood tests to monitor your kidneys before and during treatment. Drink plenty of fluids during treatment. Tell your doctor immediately if you vomit and become dehydrated.

Children and adolescents
Braftovi 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 Braftovi
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
Some medicines may affect how Braftovi 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 fungal infections (such as itraconazole, posaconazole, fluconazole)
- some medicines to treat bacterial infections (such as rifampicin, clarithromycin, telithromycin, erythromycin, penicillin)
- medicines typically used to treat epilepsy (seizures) (such as phenytoin, carbamazepine)
- medicines typically used to treat cancer (such as methotrexate, imatinib)
- medicines typically used to treat high cholesterol (such as rosuvastatin, atorvastatin)
- an herbal treatment for depression: St. John's wort
- some medicines for HIV treatment such as ritonavir, amprenavir, raltegravir, dolutegravir
- birth control medicines containing hormones
- medicines typically used to treat high blood pressure (such as diltiazem, bosentan, furosemide)
- a medicine used to treat an uneven heartbeat: amiodarone.

Braftovi with food and drink
Do not have grapefruit juice during your treatment with Braftovi. This is because it could increase Braftovi side effects.

Pregnancy, breast-feeding and fertility
Pregnancy
Braftovi is not recommended during pregnancy. It may cause 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 Braftovi, and you must continue to use reliable contraception for at least 1 month after taking your last dose. Birth control medicines containing hormones (such as pills, injections, patches, implants and certain intrauterine devices (IUDs) that release hormones) may not work as well as expected while you are taking Braftovi. You should use another reliable method of birth control such as a barrier method (e.g. condom) so you do not become pregnant while you are taking this medicine. Ask your doctor, pharmacist or nurse for advice.
Contact your doctor straightaway if you become pregnant while taking Braftovi.

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

Fertility
Braftovi may reduce sperm count in males. This could affect the ability to father a child. Talk to your doctor if this is a concern for you.

Driving and using machines
Braftovi 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 Braftovi. Talk to your doctor if you are not sure you can drive.

3. How to take Braftovi

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 Braftovi is 6 capsules of 75 mg once daily (corresponding to a daily dose of 450 mg). You will also receive treatment with another medicine, binimetinib.

If you have liver or kidney problems, your doctor may start you on a lower dose.
If you get serious side effects (such as heart, eye or bleeding problems) your doctor may lower the dose or stop treatment temporarily or permanently.

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

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

If you take more Braftovi than you should
If you take more capsules than you should, contact your doctor, pharmacist or nurse straightaway. Side effects of Braftovi such as nausea, vomiting, dehydration and blurred vision may appear or worsen. If possible, show them this leaflet and the medicine package.

If you forget to take Braftovi
If you miss a dose of Braftovi, take it as soon as you remember. However if the missed dose is more than 12 hours late, skip that dose and take your next dose at the usual time. Then continue taking your capsules at regular times as usual.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Braftovi
It is important to take Braftovi 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

Braftovi 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: Braftovi when taken with binimetinib 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

Eye problems: Braftovi, when taken with binimetinib, can cause serious eye problems such as fluid to leak under the retina in the eye, leading to detachment of different layers in the eye (retinal epithelial pigmental detachment). Call your doctor right away if you get these symptoms of eye problems:
- blurred vision, loss of vision, or other vision changes (such as coloured dots in your vision)
- halo (seeing blurred outline around objects)
- eye pain, swellling or redness

Bleeding problems: Braftovi can cause serious bleeding problems. Tell your doctor right away if you have any unusual 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

Muscle problems: Braftovi, when taken with binimetinib, 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

Other skin cancers: Treatment with Braftovi may result in a different type of skin cancer such as cutaneous squamous cell carcinoma. Usually, these skin changes (see also section 2) are confined to a small area and can be removed with surgery and treatment with Braftovi (and binimetinib) can continue without interruption. Some people taking Braftovi may also notice new melanomas. These melanomas are usually removed by surgery and treatment with Braftovi (and binimetinib) can continue without interruption.

Other side effects
Besides the serious side effects mentioned above, people taking Braftovi may also get other side effects.

Side effects when Braftovi and binimetinib are taken together

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
- high blood pressure
- 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 pain, weakness or spasm
- 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 results related to blood creatine kinase, indicating damage to the heart and muscle

Common (may affect up to 1 in 10 people)
- some types of skin tumours such as skin papilloma and basal cell carcinoma
- allergic reaction that may include swelling of the face and difficulty breathing
- changes in the way things taste
- inflammation of the eye (uveitis)
- blood clots
- 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)
- weakness and paralysis of face muscles
- inflammation of the pancreas (pancreatitis) causing severe abdominal pain

When Braftovi was used on its own in clinical trials

If you continue Braftovi on its own while the other medicine (binimetinib) is temporarily stopped based on your doctor's decision, you may get some of the side effects given in the lists above, although the frequency may change (increase or decrease).

Very common (may affect more than 1 in 10 people)
- fatigue
- feeling sick (nausea)
- being sick (vomiting)
- constipation
- skin rash of various types
- redness, skin peeling or blisters on hand and feet (called palmar-plantar erythrodysesthesia or hand and foot syndrome)
- thickening of the outer layers of the skin (hyperkeratosis)
- dry skin
- itching
- abnormal hair loss or thinning (alopecia)
- redness, chapping or cracking of the skin
- skin darkening
- lost of appetite
- difficulty sleeping (insomnia)
- headache
- problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet
- changes in the way things taste
- joint pain (arthralgia)
- muscle pain, spasm or weakness
- pain in the extremities
- back pain
- fever
- some types of benign skin tumour such as melanocytic naevus and skin papilloma
- abnormal blood tests results related to the liver

Common (may affect up to 1 in 10 people)
- allergic reaction that may include swelling of the face and difficulty in breathing
- weakness and paralysis of face muscles
- fast heart beat
- skin rash with a flat discoloured area or raised bumps like acne (dermatitis acneiform)
- peeling or scaly skin
- inflammation of joints (arthritis)
- kidney failure
- abnormal kidney test results (creatinine elevations)
- increased skin sensitivity to sunlight
- abnormal blood test result for pancreas function (lipase)

Uncommon (may affect up to 1 in 100 people)
- type of skin cancer such as basal cell carcinoma
- inflammation of the eye (uveitis)
- inflammation of the pancreas (pancreatitis) causing severe abdominal pain
- abnormal blood test result for pancreas function (amylase)

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 Braftovi

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 carton and the blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C. Store in the original package in order to protect from moisture.

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 Braftovi contains
- The active substance is encorafenib.
  Braftovi 50 mg: Each hard capsule contains 50 mg encorafenib.
  Braftovi 75 mg: Each hard capsule contains 75 mg encorafenib.
- The other ingredients are:
  - Capsule contents: copovidone (E1208), poloxamer 188, cellulose microcrystalline (E460i), succinic acid (E363), crospovidone (E1202), silica colloidal anhydrous (E551), magnesium stearate (E470b)
  - Capsule shell: gelatin (E441), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172)
  - Printing ink: shellac (E904), iron oxide black (E172), propylene glycol (E1520)

What Braftovi looks like and contents of the pack
Braftovi 50 mg hard capsules
The hard capsule (capsule) has an orange opaque cap and flesh opaque body, with a stylised “A” printed on the cap and “LGX 50mg” printed on the body.
Braftovi 50 mg is available in packs of 28 capsules (7 blisters of 4 capsules each) or 112 capsules (28 blisters of 4 capsules each). Not all pack sizes may be marketed.

Braftovi 75 mg hard capsules
The hard capsule (capsule) has a flesh coloured opaque cap and white opaque body, with a stylised “A” printed on the cap and “LGX 75mg” printed on the body.
Braftovi 75 mg is available in packs of 42 capsules (7 blisters of 6 capsules each) or 168 capsules (28 blisters of 6 capsules each). Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pierre Fabre Médicament
45, place Abel Gance
92100 Boulogne-Billancourt
France

Manufacturer
Pierre Fabre Médicament Production
Aquitaine Pharm International 1
Avenue du Béarn
64320 Idron
France

or

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: http://www.ema.europa.eu.