Braftovi

ENCORAFENIB

Hard Capsules

Reference Label: Belgium/EU-SmPC

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

AfME Markets using same as LPD: Nigeria

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▼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 is indicated:

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

BRAF V600E Mutant CRC
- in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

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

Posology

BRAF V600 Mutant Melanoma and BRAF V600E Mutant NSCLC
The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib.

Colorectal cancer
The recommended dose of encorafenib is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab.

Dose modification

Melanoma
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib (see Tables 1, 3 and 4).
For information on the posology and recommended dose modifications of binimetinib, see section 4.2 of binimetinib SmPC.

Dose reduction recommendations for encorafenib are presented in Table 1.

Table 1: Recommended dose modifications for encorafenib when used in combination with binimetinib in melanoma indication

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 100 mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100 mg 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 Tables 3 and 4), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued.

If treatment-related toxicities occur, then encorafenib and binimetinib should be dose reduced, interrupted or discontinued. Dose modifications are necessary for binimetinib only (adverse reactions primarily related to binimetinib) for the following: 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.

Colorectal cancer
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib (see Tables 2, 3 and 4).
For information on the posology and recommended dose modifications of cetuximab, see section 4.2 of cetuximab SmPC.

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Dose reduction recommendations for encorafenib are presented in Table 2.

Table 2: Recommended dose modifications for encorafenib when used in combination with cetuximab in CRC indication

Dose level	**Encorafenib dose** when used in combination with cetuximab
Starting dose	300 mg once daily
1st dose reduction	225 mg once daily
2nd dose reduction	150 mg once daily

If encorafenib is permanently discontinued, cetuximab should be discontinued.
If cetuximab is permanently discontinued, encorafenib should be discontinued.

Melanoma and colorectal cancer
Dose modifications in case of adverse reactions are provided below and in Tables 3 and 4.

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 permanently.

Table 3: Recommended dose modifications for encorafenib when used in combination with binimetinib or in combination with cetuximab 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.
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.

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Severity of adverse reaction[a]	Encorafenib
	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
• 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

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Table 4: Recommended dose modifications for encorafenib when used in combination with binimetinib or in combination with cetuximab 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 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.

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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 patients with BRAF V600 mutant unresectable or metastatic melanoma), or in combination with cetuximab (for patients with BRAF V600E mutant metastatic colorectal cancer). For additional information on warnings and precautions associated with binimetinib or cetuximab treatment, see section 4.4 of binimetinib SmPC or cetuximab SmPC.

BRAF mutation testing

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

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 decrease 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.

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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 4 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 have 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, every 2 months while on therapy and for up to 6 months following treatment discontinuation. 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 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

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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 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 dose of 300 mg once daily 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 or cetuximab. 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 4 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

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predictions for ketoconazole suggest an increase of approx. 5-fold for encorafenib AUC and 3 to 4-fold for encorafenib C_{max} after administration of encorafenib 450 and 300 mg QD, respectively. 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
In vivo, encorafenib is an inhibitor of OATP1B1, OATP1B3 and/or BCRP. Coadministration of encorafenib with OATP1B1, OATP1B3 or BCRP substrates (such as rosuvastatin, atorvastatin, methotrexate) can result in increased concentrations (see section 5.2).
In vitro, encorafenib potentially inhibits a number of other transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 (such as furosemide, penicillin) or agents that are substrates of the hepatic transporters OCT1 (such as, bosentan) or substrates of P-gp (e.g. posaconazole) may also have increased exposure.
Therefore, these agents, substrates of transporters should be 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).

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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.

The safety of encorafenib (300 mg orally once daily) in combination with cetuximab (dosed as per its SmPC) was evaluated in 216 patients with BRAF V600E-mutant metastatic colorectal cancer, based on the phase III study ARRAY-818-302. The most common ADRs (>25%) reported in this population were: fatigue, nausea, diarrhoea, dermatitis acneiform, abdominal pain, arthralgia/musculoskeletal pain, decreased appetite, rash and vomiting.
The rate of all study drug discontinuation due to any adverse reaction was 1.9 % in patients treated with encorafenib 300 mg in combination with cetuximab.

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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 5: Adverse reactions

Frequency	**Encorafenib single agent 300 mg (n = 217)**	**Encorafenib 450 mg in combination with binimetinib (n = 274)**	**Encorafenib 300 mg in combination with cetuximab (n = 216)**
Neoplasms benign, malignant and unspecified			
Very common	Skin papilloma[*] Melanocytic nevus		Melanocytic naevus
Common	cuSCC [a] New Primary Melanoma[*]	cuSCC[a] Basal cell carcinoma[*] Skin papilloma[*]	cuSCC[a] Skin papilloma[*] New Primary Melanoma[*]
Uncommon	Basal cell carcinoma		Basal cell carcinoma
Blood and lymphatic system disorders			
Very common		Anaemia	
Immune system disorders			
Common	Hypersensitivity[b]	Hypersensitivity[b]	Hypersensitivity[b]
Metabolism and nutrition disorders			
Very common	Decreased appetite		Decreased appetite
Psychiatric disorders			
Very common	Insomnia		Insomnia
Nervous system disorders			
Very common	Headache[*] Neuropathy peripheral[*] Dysgeusia[*]	Neuropathy peripheral[*] Dizziness[*] Headache[*]	Neuropathy peripheral[*] Headache[*]
Common	Facial paresis[c]	Dysgeusia[*]	Dizziness[*] Dysgeusia
Uncommon		Facial paresis[c]	
Eye disorders			
Very common		Visual impairment[*] RPED [*]	
Common		Uveitis [*]	
Uncommon	Uveitis[*]		
Cardiac disorders			
Common	Supraventricular tachycardia[d]	LVD[h]	Supraventricular tachycardia[d]
Vascular disorders			
Very common		Haemorrhage[i] Hypertension [*]	Haemorrhage[i]
Common		VTE[j]	

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Gastrointestinal disorders			
Very common	Nausea Vomiting[*] Constipation	Nausea Vomiting[*] Constipation Abdominal pain[*] Diarrhoea[*]	Nausea Vomiting Constipation Abdominal pain[*] Diarrhoea[*]
Common		Colitis[k]	
Uncommon	Pancreatitis[*]	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[*]	Dermatitis acneiform[*] Rash[*] Dry skin[*] Pruritus[*]
Common	Dermatitis acneiform[*] Skin exfoliation[f] Photosensitivity[*]	Dermatitis acneiform[*] PPES Erythema[*] Panniculitis[*] Photosensitivity[*]	Skin hyperpigmentation PPES Hyperkeratosis[*] Alopecia Erythema[e]
Uncommon			Skin exfoliation[f]
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	Arthralgia/Musculoskeletal pain[*] Myopathy/Muscular disorder[*] Pain in extremity Back pain
Common	Arthritis[*]		
Uncommon		Rhabdomyolysis	
Renal and urinary disorders			
Common	Renal failure[*]	Renal failure[*]	Renal failure[*]
General disorders and administration site conditions			
Very common	Fatigue[*] Pyrexia[*]	Fatigue[*] Pyrexia[*] Peripheral oedema[m]	Fatigue[*] Pyrexia[*]

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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	Blood creatinine increased* Transaminase increased*
Uncommon	Amylase increased		Amylase increased Lipase increased

*composite terms which included more than one preferred term
[a] includes, but not limited to, keratoacanthoma and squamous cell carcinoma
[b] includes, but not limited to, angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, urticaria and anaphylactic reaction
[c] includes facial nerve disorder, facial paralysis, facial paresis
[d] includes but not limited to extrasystoles and sinus 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, but not limited to, 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, but not limited to, fluid retention, peripheral oedema and 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
Melanoma
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).

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Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, cuSCC including keratoacanthoma was observed in 1.4% (3/216) of patients. The times to first event of cuSCC (all grades) were 0.5, 0.6 and 3.6 months for these 3 patients.

New primary melanoma
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.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, new primary melanoma events occurred in 1.9% of patients (4/216) and were reported as Grade 2 in 0.9% (2/216) of patients and Grade 3 in 0.9% (2/216) of patients.

Ocular events
Melanoma
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 in melanoma patients (see section 4.8 of binimetinib SmPC).

Haemorrhage
Melanoma
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.

Colorectal cancer
Haemorrhagic events were observed in 21.3% (46/216) of patients treated with encorafenib 300 mg in combination with cetuximab; 1.4% (3/216) of patients were Grade 3 events and one fatal case was reported. Dose interruptions or dose reductions were required in 1.9% (4/216) of patients. Haemorrhagic events led to treatment discontinuation in 1 patient (0.5%).
The most frequent haemorrhagic events were epistaxis in 6.9% (15/216) of patients, haematochezia in 2.8% (6/216), rectal haemorrhage in 2.8% (6/216) of patients and haematuria in 2.8% (6/216) of patients.

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

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

Pancreatitis
Melanoma
In the pooled Combo 450 population, pancreatic enzyme elevation, mostly asymptomatic, was reported. 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 in (0.4 %) 1/274 of patients.

Colorectal cancer
In the population treated with encorafenib 300 mg in combination with cetuximab, pancreatitis grade 3 with lipase and amylase increased events were reported in 1 patient (0.5%) and led to dose interruption.

Dermatologic reactions
Rash
Melanoma
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.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, rash occurred in 30.6% (66/216) of patients. Most events were mild, with Grade 3 event reported in 0.5% (1/216) of patients. Rash led to dose interruption in 0.5% (1/216) of patients.

Palmar-plantar erythrodysaesthesia syndrome (PPES)
Melanoma
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.

Colorectal cancer
In the population treated with encorafenib 300 mg in combination with cetuximab, PPES was reported in 5.1% (11/216) of patients. Most of PPES adverse reactions were either Grade 1 in 3.7 % (8/216). Grade 2 events were reported in 0.9% (2/216) of patients, and Grade 3 in 0.5% (1/216) of patients. No dose interruption, dose modification or treatment discontinuation was required.

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

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, dermatitis acneiform occurred in 33.3% (72/216) of patients and was mostly Grade 1 (25.5% (55 /216) of patients), or 2 (6.9% (15 /216) of patients). Dose reduction or interruption was reported in 2.3 % (5/216) of patients. No treatment discontinuation was reported. Dermatitis acneiform was generally reversible.

Photosensitivity
Melanoma
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
Melanoma
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 in melanoma patients (see section 4.8 of binimetinib SmPC).

Renal dysfunction
Melanoma
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.

Colorectal cancer
Blood creatinine elevation was reported in 2.8% (6/216) of patients treated with encorafenib 300 mg in combination with cetuximab. All were mild except one event of Grade 4. Renal failure events were Grade 3 or 4 and reported as acute kidney injury in 1.9 % (4/216) of patients and renal failure in 0.5% (1/216) of patients.

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Liver laboratory abnormality
Melanoma
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)

Colorectal cancer
The incidence of increased transaminases in patients treated with encorafenib 300 mg in combination with cetuximab was 8.8% (19/216) of patients, with Grade 3 in 1.4% (3/216) of patients.

Gastrointestinal disorders
Melanoma
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 treatment 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.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, diarrhoea was observed in 38.4% (83/216) of patients and was Grade 3 in 2.8% (6/216) of patients. Diarrhoea led to treatment discontinuation in 0.5% (1/216) of patients and to dose interruption or dose modification in 3.7% (8/216) of patients.

Abdominal pain was reported in 36.6% (79/216) of patients and was Grade 3 in 5.1% (11/216) of patients. Nausea occurred in 38.0% (82/216) of patients with Grade 3 observed in 0.5% (1/216) of patients. Vomiting occurred in 27.3% (59/216) of patients with Grade 3 reported in 1.4 % (3/216) of patients. Constipation occurred in 18.1% (39/216) of patients and was Grade 1 or 2.

Gastrointestinal disorders were typically managed with standard therapy.

Anaemia
Melanoma
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
Melanoma
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.

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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.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, headache occurred in 20.4% (44/216) of patients and was Grade 1 or 2.

Fatigue
Melanoma
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.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab, fatigue was reported in 56.9% (123/216) of patients including Grade 3 in 7.9% (17/216) of patients.

Special populations

Elderly
Melanoma
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.

Colorectal cancer
In patients treated with encorafenib 300 mg in combination with cetuximab (n=216), 134 patients (62 %) were < 65 years old, 62 patients (28.7%) were 65-74 years old and 20 patients (9.3%) were aged ≥ 75. The most common AEs reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included, anaemia, asthenia, decreased appetite and dyspnoea.

In both melanoma and colorectal cancer populations, due to a very small number of patients treated in the age subgroup of patients aged ≥ 75 years, differences in the incidence of AEs compared to patients aged < 75 years could not be assessed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local requirements.

4.9 Overdose

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.

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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 agents, protein kinase inhibitors, ATC code: L01EC03

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 and BRAF V600E mutant colorectal cancer 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*.

Combination with cetuximab
One of the main mechanisms of resistance of BRAF-mutant CRC to RAF inhibitors has been identified as the re-activation of EGFR with bypassing signal transduction via BRAF. Combinations of a BRAF inhibitor, e.g.encorafenib and agents targeting EGFR, e.g. cetuximab have shown to improve anti-tumour efficacy in non-clinical models.

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

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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 6 and Figure 1 summarise the PFS and other efficacy results based on central review of the data by a blinded independent radiology committee.

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

Table 6: 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		

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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)

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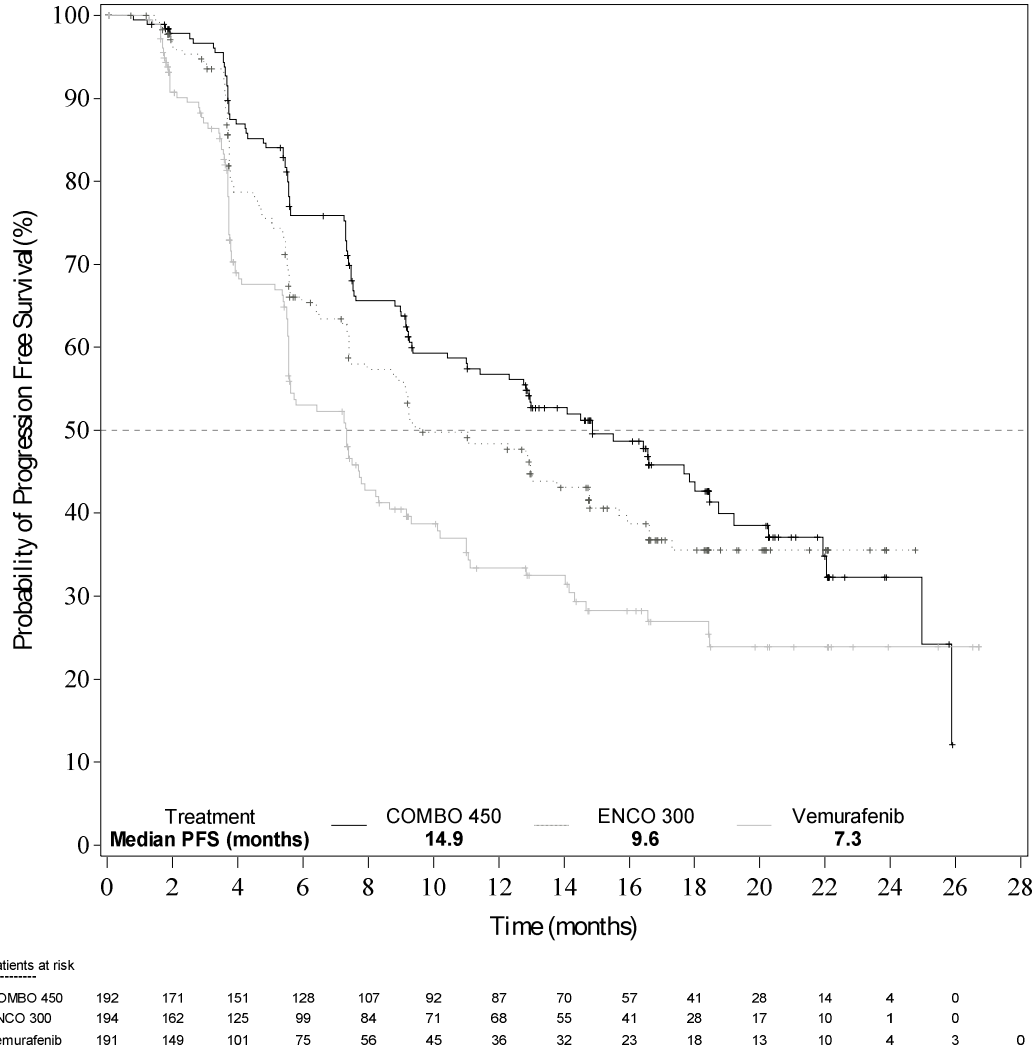
Figure 1 Study CMEK162B2301, Part 1: Kaplan-Meier plot of progression-free survival by independent central review (cut-off date: 19 May 2016)



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 7 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).

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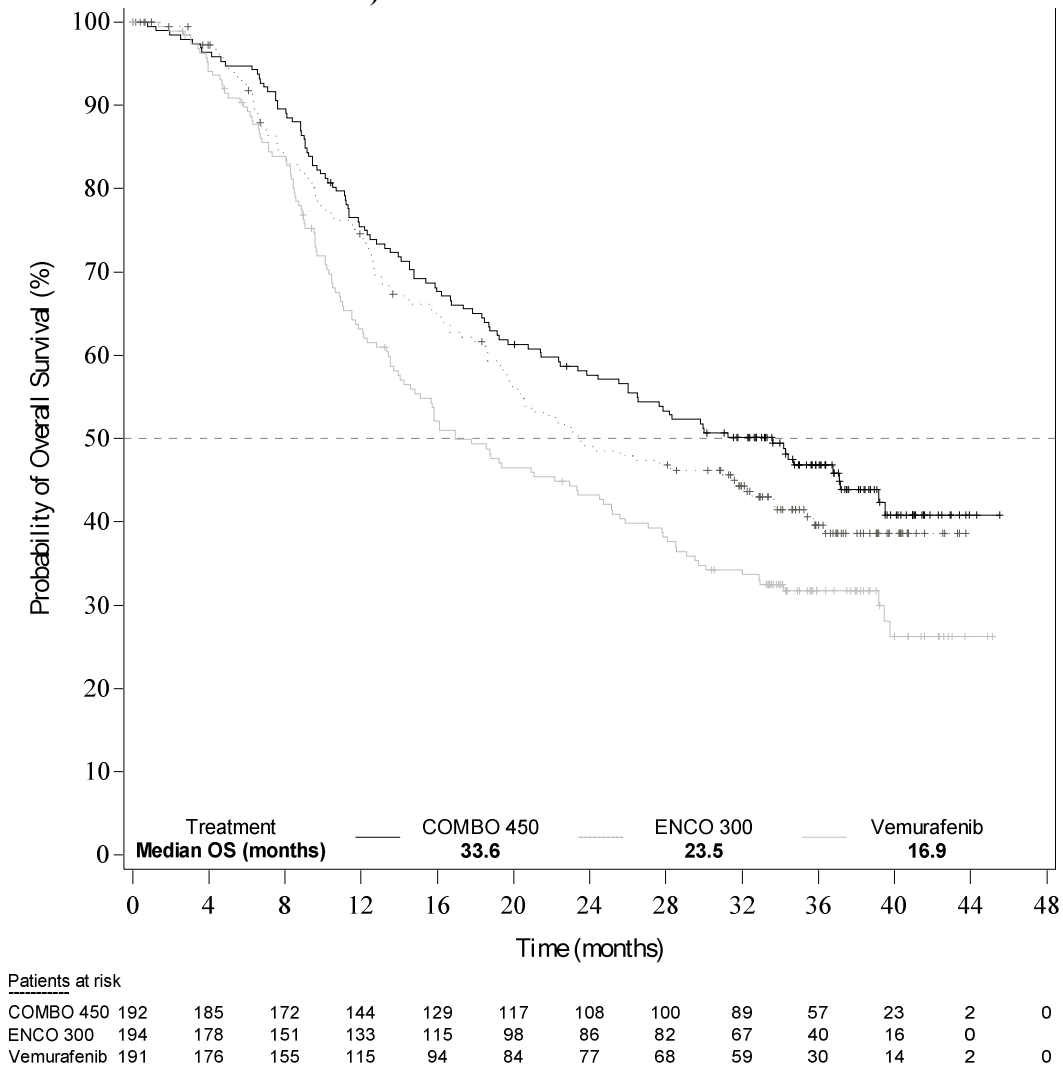
Table 7: Study CMEK162B2301, Part 1: Overall survival interim results (cut-off date: 7 November 2017)

	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)



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

BRAF V600E Mutant Metastatic Colorectal Cancer - Study ARRAY-818-302
Encorafenib in combination with cetuximab was evaluated in a randomised, active-controlled, open-label, multicentre trial (ARRAY 818-302 BEACON CRC). Eligible patients were required to have BRAF V600E mutant metastatic colorectal cancer that had progressed after 1 or 2 prior regimens. Enrolled patients were eligible to receive cetuximab per locally approved label with regards to tumour RAS status. Prior use of RAF inhibitors, MEK inhibitors or EGFR inhibitors was prohibited. Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status, prior use of irinotecan and cetuximab source.

A total of 665 patients were randomised (1:1:1) to receive encorafenib 300 mg orally daily in combination with cetuximab dosed as per its approved SmPC (n=220), or encorafenib 300 mg orally daily in combination with binimetinib 45 mg orally twice daily and cetuximab dosed as per its approved SmPC (n=224) or Control (irinotecan with cetuximab or irinotecan/5-fluorouracil/folinic acid (FOLFIRI) with cetuximab, n= 221). Treatment continued until disease progression or unacceptable toxicity.

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The efficacy outcome measures were overall survival (OS) and overall response rate (ORR) as assessed by a blinded independent central review committee (BIRC), comparing encorafenib 300 mg in combination with cetuximab versus Control. Other efficacy measures are summarised in Table 8 below.

The median age of patients was 61 years (range 26-91), 47 % were male and 83% were white. 51% of patients had baseline ECOG performance status of 0, and 51% received prior irinotecan. 46.8% of patients had at least 3 organs with tumour involvement at baseline.
The median duration of exposure was 3.2-months in patients treated with encorafenib 300 mg in combination with cetuximab, and 1.4 months in patients treated with irinotecan/cetuximab or FOLFIRI/cetuximab (Control arm). In patients treated with the combination of encorafenib 300 mg and cetuximab, the median relative dose intensity (RDI) was 98% for encorafenib and 93.5% for cetuximab. In the control arm, the median RDI was 85.4% for cetuximab, 75.7% for irinotecan and in the subset of patients who received Folinic acid and 5-FU, the median RDI was 75.2% and 75% respectively.

Encorafenib 300 mg in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR and PFS compared to Control. Efficacy results are summarised in Table 8 and Figures 3 and 4.

The efficacy results based on investigator assessment were consistent with the independent central assessment.

Table 8: Study ARRAY-818-302: Efficacy Results

	Encorafenib with cetuximab	**Irinotecan with cetuximab or FOLFIRI with cetuximab (Control)**
Cut-off date: 11 February 2019 (Primary analysis)		
OS		
Number of patients[a]	220	221
Number of events (%)	93 (42.3)	114 (51.6)
Median, months (95% CI)	8.4 (7.5-11.0)	5.4 (4.8, 6.6)
HR (95% CI)[b,c] (vs Control) p-value[b,c]	0.60 (0.41-0.88) 0.0002	
Median duration of follow-up, months (95% CI)	7.6 (6.4, 9.20)	7.2 (6.1, 8.1)
ORR (per BIRC)		
Number of patients[e]	113	107
ORR n (%) (95% CI)[f]	23 (20.4) (13.4, 29.0)	2 (1.9) (0.2, 6.6)
P-value[b,d,g]	<0.0001	
CR, n (%)	6 (5.3)	0
PR, n (%)	17 (15.0)	2 (1.9)
SD, n (%)	57 (50.4)	26 (24.3)
DCR, n (%) (95% CI)[f]	84 (74.3) (65.3, 82.1)	33 (30.8) (22.3, 40.5)

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PFS (per BIRC)		
Number of patients[a]	220	221
Number of events (%)	133 (60.5)	128 (57.9)
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.5, 1.7)
HR (95% CI)[b,c] P-value[b,d]	0.40 (0.30, 0.55 < 0.0001	
Updated analysis, cut-off date: 15 August 2019		
OS		
Number of patients[a]	220	221
Number of events (%)	128 (58.2)	157 (71.0)
Median, months (95% CI)	9.3 (8.0, 11.3)	5.9 (5.1, 7.1)
HR (95% CI)[b] (vs Control) p-value[b,d,h]	0.61 (0.48, 0.77) < 0.0001	
Median duration of follow-up, months (95% CI)	12.3 (11.1, 14.1)	12.9 (10.9, 14.6)
ORR (per BIRC)		
Number of patients[a]	220	221
ORR n (%) (95% CI)[f]	43 (19.5) (14.5, 25.4)	4 (1.8) (0.5, 4.6)
p-value[b,d,g,h]	<0.0001	
CR, n (%)	7 (3.2)	0
PR, n (%)	36 (16.4)	4 (1.8)
SD, n (%)	117 (53.2)	59 (26.7)
DCR, n (%) (95% CI)[f]	167 (75.9) (69.7, 81.4)	69 (31.2) (25.2, 37.8)
PFS (per BIRC)		
Number of patients[a]	220	221
Number of events (%)	167 (75.9)	147 (66.5)
Median PFS, months (95% CI)	4.3 (4.1, 5.5)	1.5 (1.5, 1.9)
HR (95% CI)[b] P-value[b,d, h]	0.44 (0.35, 0.55) < 0.0001	

CI = Confidence interval; CR = Complete response; HR = Hazard ratio; ORR = Overall response rate; OS = Overall survival; PR = Partial response; SD = Stable disease, DCR: Disease control rate (CR+PR+SD+Non-CR/Non-PD; Non-CR/Non-PD applies only to patients with a non-measurable disease who did not achieve CR or have PD)

[a] Randomised Phase 3, Full Analysis Set
[b] Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization
[c] Repeated CI derived using Lan DeMets O'Brien-Fleming boundaries associated with the observed information fraction at the interim analysis
[d] 1-sided
[e] Among the first 331 randomised patients
[f] Clopper-Pearson's method
[g] Cochran Mantel-Haenszel test
[h] Nominal p-value

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Figure 3: Study ARRAY-818-302: Kaplan-Meier plot of Overall Survival (cut-off date: 11 February 2019)

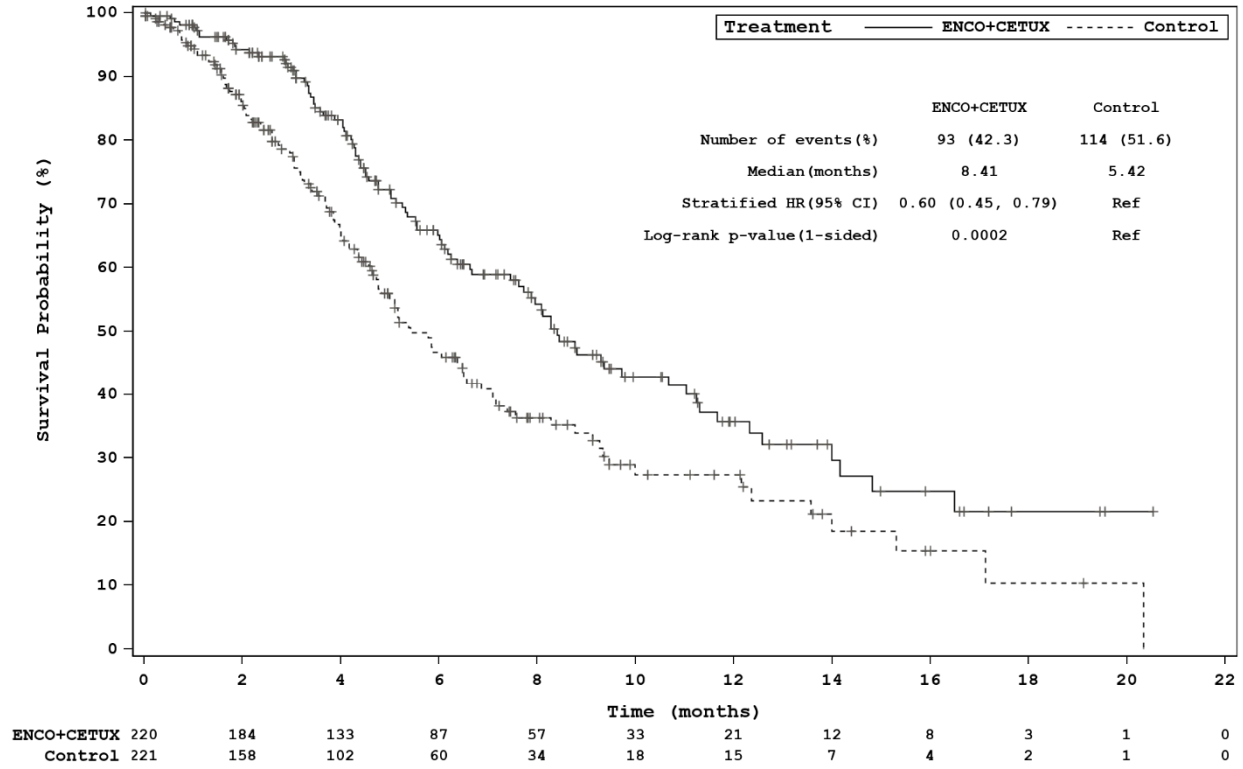
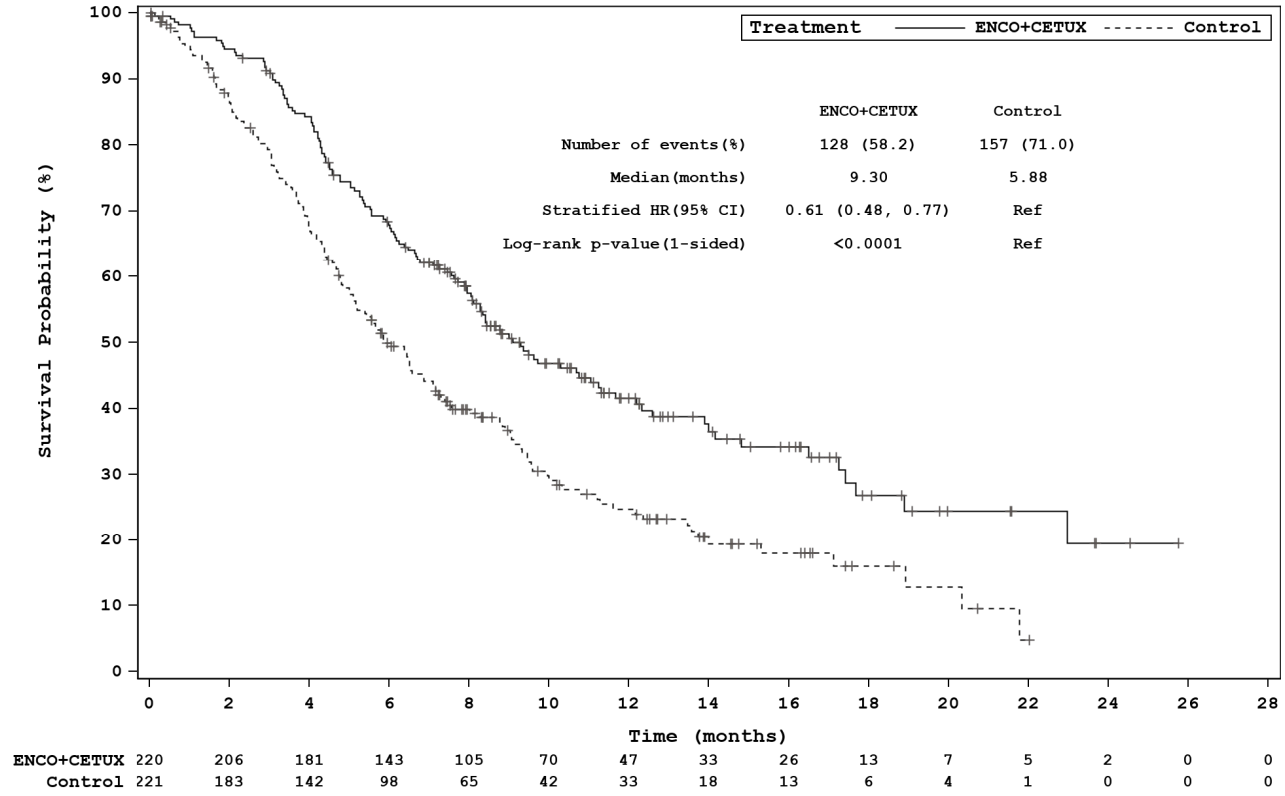


Figure 4: Study ARRAY-818-302: Kaplan-Meier plot of Overall Survival (cut-off date: 15 August 2019)



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Cardiac Electrophysiology
In the safety analysis of the Phase 3 (ARRAY-818-302) safety set in colorectal indication, the incidence of new QTcF prolongation >500 ms was 3.2% (7/216) and QTcF prolongation of >60 ms compared to pre-treatment values was observed in 8.8% (19/216) of patients of the encorafenib + cetuximab arm (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).

The European Medicines Agency has waived the obligation to submit the results of studies with encorafenib in all subsets of the paediatric population in colorectal carcinoma (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, and in adult patients with metastatic colorectal cancer with a BRAF V600E 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).

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Medicinal product interactions

No drug drug interaction was evidenced between encorafenib and cetuximab.

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
Repeated administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with a single dose of rosuvastatin (a OATP1B1, OATP1B3 and BCRP substrate) increased rosuvastatin Cmax by 2.7-fold and AUC by 1.6-fold indicating a mild inhibition of OATP1B1, OATP1B3 and/or BCRP 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. at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut 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

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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 no clinically relevant differences in encorafenib PK between Asians and non Asians . There are insufficient data to evaluate potential differences in the exposure of encorafenib in other races 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 determined in the 13-week study was more than 10-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 13-week rat toxicology studies, encorafenib treatment at 6 mg/kg/d (dose level more than 5 times the human exposure at the therapeutic 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.

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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

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

6.4 Special precautions for storage

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

Each pack contains either 28 or 112 hard capsules in polyamide/aluminium/PVC/aluminium/ PET/paper perforated unit dose blisters.
Not all pack sizes or strengths may be marketed.

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Braftovi 75 mg hard capsules

Each pack contains either 42 or 168 hard capsules in polyamide/aluminium/PVC/aluminium/ PET/paper perforated unit dose blisters.
Not all pack sizes or strengths may be marketed.

6.6 Special precautions for disposal

Keep out of the sight and reach of children.

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

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

7. FURTHER INFORMATION

MANUFACTURED BY:

Catalent Pharma Solutions LLC
14 Schoolhouse Road - Somerset, NJ 08873, US

PACKAGED AND RELEASED BY:

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

8. PRESCRIPTION STATUS

Prescription only medicine

9. DATE OF REVISION OF THE TEXT

November 2023

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Document Approval Record

Document Name:	Braftovi 50 75 mg HC LPD Nigeria (Pierre Fabre)
Document Title:	Braftovi 50 75 mg HC LPD Nigeria (USPI - LAB-1428-3.0 - New Indication (NSCLC 1L) Only)

Signed By:	Date(GMT)	Signing Capacity
Ongare, Louise Akeyo	16-Nov-2023 09:13:03	Regulatory Affairs Approval

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