AUSTRALIAN PRODUCT INFORMATION
BRAFTOVI® (encorafenib) capsules

1. NAME OF THE MEDICINE

Encorafenib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BRAFTOVI 50 mg hard capsule contains encorafenib 50 mg.

Each BRAFTOVI 75 mg hard capsule contains encorafenib 75 mg.

For the list of excipients, see section 6.1 *List of excipients.*

3. PHARMACEUTICAL FORM

BRAFTOVI 50 mg hard capsules
Swedish orange opaque cap and flesh-coloured opaque body, printed with a stylised "A" on the cap and "LGX 50 mg" 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 75 mg" on the body. The length of the capsule is approximately 23 mm.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Melanoma
Encorafenib in combination with binimetinib, is indicated for the treatment of adult patients who have unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, as detected by a validated test.

Colorectal Cancer (CRC)
Encorafenib, in combination with cetuximab is indicated for the treatment of adult patients who have metastatic colorectal cancer (mCRC) with a *BRAF* V600E mutation, as detected by a validated test, and who have received prior systemic therapy.

Non-small cell lung cancer (NSCLC)
Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with metastatic non-small cell lung cancer with a BRAF V600E mutation.

4.2. DOSE AND METHOD OF ADMINISTRATION

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

BRAF mutation testing
Prior to treatment with encorafenib, the BRAF V600 mutation status of a patient's melanoma, colorectal cancer or NSCLC must be confirmed by a validated test, conducted by an experienced laboratory (see section 5.1 Pharmacodynamic properties, Clinical trials).The efficacy and safety of encorafenib have been established only in patients with melanoma tumours expressing BRAF V600E and V600K mutations, colorectal tumours expressing a BRAF V600E mutation or NSCLC expressing a BRAF V600E mutation. Encorafenib should not be used in patients with wild type BRAF malignant melanoma, wild type BRAF colorectal cancer or wild-type BRAF NSCLC.

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

For information on binimetinib dosage, refer to section 4.2 *Dose and method of administration* of the binimetinib Product Information (PI).

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

For information on cetuximab dosage, refer to section 4.2 *Dose and method of administration* of the cetuximab PI.

Administration
Encorafenib capsules should be swallowed whole with water, with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided (see section 4.5 *Interactions with other medicines and other forms of interactions*).

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

Missed dose
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 after administration
If a patient vomits after taking encorafenib, the patient should not take an additional dose. The patient should take the next scheduled dose.

Dose modification
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation. Recommended encorafenib dose levels for dose reduction are different in melanoma or NSCLC (Table 1) compared to mCRC (Table 2). Dose modification recommendations in case of adverse reactions (regardless of treatment indication) are presented in Table 3.

Melanoma and NSCLC
If treatment-related toxicities occur when encorafenib is used in combination with binimetinib, dose modification should generally be undertaken for both drugs.

The following adverse reactions are more likely to be related to binimetinib than encorafenib: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation, rhabdomyolysis and venous thromboembolism. If one of these toxicities occurs, consider dose modification of binimetinib alone.

For information on dosage and recommended dose modifications for binimetinib, refer to section 4.2 *Dose and method of administration* of the binimetinib PI.

Recommended dose levels for encorafenib dose reduction (when used in combination with binimetinib for the treatment of melanoma or NSCLC) are presented in Table 1.

Table 1: Melanoma or NSCLC indication - recommended dose levels for encorafenib dose reduction

Dose level	**Encorafenib dose** (when used in combination with binimetinib)
Starting dose	450 mg (six 75 mg capsules) once daily
1st dose reduction	300 mg (four 75 mg capsules) once daily
2nd dose reduction	225 mg (three 75 mg capsules) once daily
Subsequent modification	For Melanoma and NSCLC indication: Permanently discontinue encorafenib (and binimetinib) if unable to tolerate encorafenib 225 mg (three 75 mg capsules) once daily.

If encorafenib is temporarily interrupted, interrupt binimetinib.

If binimetinib is temporarily interrupted, reduce encorafenib to 300 mg once daily during the time of binimetinib dose interruption. Administration of encorafenib at a dose of 450 mg once daily as a single agent is not well tolerated, and not recommended.

If encorafenib is permanently discontinued, then discontinue binimetinib.
If binimetinib is permanently discontinued, encorafenib may be continued at a reduced dose of 300 mg, depending on the individual clinical benefit.

Colorectal cancer
The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib.
For information on dosage and recommended dose modifications for cetuximab, refer to section *4.2 Dose and method of administration* of the cetuximab PI.

Recommended dose levels for encorafenib dose reduction (when used in combination with cetuximab for the treatment of mCRC) are presented in Table 2.

Table 2: mCRC indication - recommended dose levels for encorafenib dose reduction

Dose level	**Encorafenib dose** (when used in combination with cetuximab)
Starting dose	300 mg (four 75 mg capsules) once daily
1st dose reduction	225 mg (three 75 mg capsules) once daily
2nd dose reduction	150 mg (two 75 mg capsules) once daily

If encorafenib is permanently discontinued, cetuximab should be discontinued.

If cetuximab is permanently discontinued, encorafenib should be discontinued.

All indications
Dose modification recommendations in case of adverse reactions (regardless of treatment indication) are presented in Table 3.

Table 3: Recommended dose modification for encorafenib for adverse reactions (all indications)

Severity of adverse reaction[a]	**Recommended encorafenib dose modification**
New Primary Malignancies[b]	
New primary non-cutaneous, RAS mutation-positive malignancies	
• Any grade	Consider permanently discontinuing encorafenib.
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, withhold encorafenib for up to 6 weeks. Repeat ophthalmic monitoring within 2 weeks: – If uveitis is Grade 1 and it improves to Grade 0, then resume at the same dose.

	– If uveitis is Grade 2 or Grade 3 and it improves to Grade 0 or 1, then resume at a reduced dose. If not improved within 6 weeks, repeat ophthalmic monitoring and permanently discontinue encorafenib.
• Grade 4	Permanently discontinue encorafenib and follow up with ophthalmologic monitoring.
QTc prolongation	
• First or second occurrence of QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Withhold encorafenib and monitor as described in section 4.4 *Special warnings and special precautions for use.* Resume encorafenib at a reduced dose when QTcF ≤ 500 ms.
• Third occurrence of QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Permanently discontinue encorafenib.
• QTcF > 500 ms and increased by > 60 ms from pre-treatment value	Permanently discontinue encorafenib (see monitoring in section 4.4 *Special warnings and special precautions for use)*.
Cutaneous reactions	
• Grade 2	Maintain encorafenib. If rash worsens or does not improve within 2 weeks with treatment, withhold encorafenib until Grade 0 or 1 and then resume at the same dose.
• Grade 3	Withhold encorafenib dose until improved to Grade 0 or 1 and resume at the same dose if first occurrence, or resume at a reduced dose if recurrent Grade 3.
• Grade 4	Permanently discontinue encorafenib.
Palmar-plantar erythrodysaesthesia syndrome (PPES)	
• Grade 2	Maintain encorafenib and institute supportive measures such as topical therapy. If not improved despite supportive therapy within 2 weeks, withhold encorafenib until improved to Grade 0 or 1 and resume treatment at the same dose level or at a reduced dose.
• Grade 3	Withhold encorafenib and institute supportive measures such as topical therapy and reassess the patient weekly. Resume at the same dose level or at a reduced dose level when improved to Grade 0 or 1.
Liver laboratory abnormalities	
• Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase	Maintain encorafenib dose. If no improvement within 4 weeks, withhold encorafenib until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resume at the same dose.

(ALT) > 3x – ≤ 5x upper limit of normal (ULN))	
• First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Withhold encorafenib for up to 4 weeks: – If improved to Grade 0 or 1 or to baseline levels, encorafenib can be resumed at a reduced dose. – If not improved, permanently discontinue encorafenib.
• First occurrence of Grade 4 (AST or ALT > 20 ULN)	Either withhold encorafenib for up to 4 weeks: – If improved to Grade 0 or 1 or to baseline levels, encorafenib can be resumed at a reduced dose. – If not improved, permanently discontinue encorafenib. Or, permanently discontinue encorafenib
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Consider permanently discontinuing encorafenib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Permanently discontinue encorafenib.
Other[c]	
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Withhold encorafenib for up to 4 weeks – If improved to Grade 0 or 1 or baseline levels, then resume at a reduced dose. – If not improved, permanently discontinue encorafenib.
• First occurrence of any Grade 4 adverse reaction	Either withhold encorafenib for up to 4 weeks: – If improved to Grade 0 or 1 or to baseline levels, then resume at a reduced dose. – If not improved, permanently discontinue encorafenib. Or, permanently discontinue encorafenib.
• Recurrent Grade 3 adverse reactions	Consider permanently discontinuing encorafenib.
• Recurrent Grade 4 adverse reactions	Permanently discontinue encorafenib.

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

[b] Dose modification of encorafenib is not required for new primary cutaneous malignancies.

[c] Dose modification of encorafenib is not required for events attributable to binimetinib (see paragraph above Table 1).

Special populations

Hepatic impairment

Patients with mild to severe hepatic impairment may have increased encorafenib exposure (see section 5.2 *Pharmacokinetic properties*). 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 requirement for dose adjustment cannot be determined for patients with severe renal impairment (see section 4.4 *Special warnings and special precautions for use* and section 5.2 *Pharmacokinetic properties*).

Elderly patients (65 years and older)

No dose adjustment is required for elderly patients (see section 5.2 *Pharmacokinetic properties*).

Children and adolescents (< 18 years)

The safety and efficacy of encorafenib have not been established in patients below the age of 18 years. There are no data available.

4.3. CONTRAINDICATIONS

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

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Before initiating treatment with encorafenib in combination with binimetinib, or encorafenib in combination with cetuximab, the PI for the relevant combination partner drug must be reviewed. Information on warnings and precautions specific to binimetinib or cetuximab treatment are described in those documents.

Assessment of *BRAF* mutation status

When assessing the *BRAF* mutation status of the tumour, it is important that a well-validated and robust test is used to minimise false-positive and false-negative determinations. *In vitro* experiments have demonstrated paradoxical activation of MAP-kinase signalling and increased cell proliferation in melanoma *BRAF* wild-type cell lines when they are exposed to *BRAF*

inhibitors. Giving *BRAF* inhibitors to patients who have *BRAF* wild-type tumours may lead to accelerated tumour growth.

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

Patients with melanoma or NSCLC who have brain metastases
There are limited efficacy data on the use of the combination of encorafenib and binimetinib in patients with a *BRAF* V600 mutant melanoma or BRAF V600E mutant NSCLC with brain metastases (see section 5.1 *Pharmacodynamic properties*).

New primary malignancies
New primary malignancies (cutaneous and non-cutaneous) have been observed in patients treated with *BRAF* inhibitors, whether administered as a single agent or used in combination.

Cutaneous malignancies
Cutaneous malignancies such as cutaneous squamous cell carcinoma 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 *Adverse effects (undesirable effects)*).

Dermatological 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 by excision and dermatopathological 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 full blood counts prior to initiation, during and at the end of treatment as clinically appropriate. Consider permanently discontinuing 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.

Haemorrhage
Haemorrhages, including major haemorrhagic events, can occur with encorafenib (see section 4.8 *Adverse effects (undesirable effects)*). The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ≥ 3

haemorrhagic events can be managed with dose interruption, or treatment discontinuation and as clinically indicated (see section 4.2 *Dose and method of administration*).

Ocular toxicities
Ocular toxicities including uveitis, iritis and iridocyclitis can occur when encorafenib is administered (see section 4.8 *Adverse effects (undesirable effects)*. Some ocular toxicities (RPED and RVO) are more likely to be related to coadministered binimetinib (see section 4.2 *Dose and method of administration*).

Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmological examination is recommended. Dose modification advice for ocular toxicities is described in section 4.2 *Dose and method of administration*.

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. Encorafenib may cause mild increases in heart rate and small increases in QTc interval (see section 5.1 *Pharmacodynamic properties*).

There are insufficient data to exclude a clinically significant, exposure-dependent QT prolongation.

Due to the potential risk for QT prolongation, correct serum electrolyte abnormalities (including magnesium, potassium and calcium) and review other risk factors for QT prolongation (e.g. control of congestive heart failure and bradyarrhythmias, and concurrent administration of other medicinal products associated with QT prolongation) before treatment initiation and during treatment.

Perform an electrocardiogram (ECG) 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, treatment interruption or treatment discontinuation with correction of abnormal electrolytes and control of risk factors (see section 4.2 *Dose and method of administration*).

Left ventricular dysfunction
Left ventricular dysfunction (LVD), defined as symptomatic or asymptomatic decreases in ejection fraction, has been reported when encorafenib is used in combination with binimetinib.

Assess LVEF (left ventricular ejection fraction) by echocardiogram or multi-gated acquisition (MUGA) scan before initiating encorafenib in combination with binimetinib, one month after initiation and then at approximately 3-month intervals or more frequently as clinically indicated

while on treatment. If LVD occurs during treatment, see section 4.2 *Dose and method of administration* of binimetinib PI.

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 limit of normal. In these patients, binimetinib should be used with caution. For any symptomatic LVD, Grade 3 or 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.

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

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 *Pharmacokinetic properties*).

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 *Dose and method of administration*).

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 section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties). 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 3 in section 4.2 Dose and method of administration). Patients should ensure adequate fluid intake during treatment.

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

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

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

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 Interactions with other medicines and other forms of interactions).

Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interaction was identified between encorafenib and cetuximab, or between encorafenib and binimetinib.

Effects of other medicinal products 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).

<u>CYP3A4 inhibitors</u>
Co-administration of strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors with single doses of encorafenib in healthy volunteers resulted in an increase in overall (AUC, 3-

and 2-fold higher, respectively) and peak (C_{max}, 68.3% and 44.6% higher, respectively) encorafenib exposure.

Concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity). Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice. 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.

The safety and tolerability of encorafenib should be carefully monitored for patients in whom concomitant use of a strong or moderate CYP3A4 inhibitor is deemed necessary.

CYP3A4 inducers

The effect of co-administering a strong CYP3A4 inducer on encorafenib exposure has not been studied in a dedicated trial however, a reduction in encorafenib exposure is likely and may result in compromised efficacy of encorafenib. Examples of strong CYP3A4 inducers include, but are not limited to carbamazepine, rifampicin, phenytoin and St. John's Wort. Alternative agents with no to moderate CYP3A induction should be considered.

Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with modafinil, a moderate CYP3A inducer, decreased encorafenib steady-state AUC by 24% and C_{max} by 20%, compared to no co-administration with modafinil.

P-gp inhibitors and inducers

Encorafenib is a substrate of P-glycoprotein (P-gp). While oral bioavailability might not be significantly affected by P-gp inhibitors or inducers because of the predicted high intestinal permeability, distribution into the central nervous system may be increased by P-gp inhibitors.

Effects of encorafenib on other medicinal products

CYP and UGT substrates

Encorafenib is a strong inducer of CYP3A4. *In vitro*,encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9 and CYP3A4/5, a relatively less potent inhibitor of CYP1A2, CYP2C8, CYP2C19 and CYP2D6, and a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes.

Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with a single dose of CYP probe substrate cocktail:

- reduced midazolam 2 mg (CYP3A4 substrate) AUC by 82% and Cmax by 74 %
- decreased omeprazole 20 mg (CYP2C19 substrate) AUC by 17 % and did not change Cmax
- increased caffeine 50 mg (CYP1A2 substrate) AUC by 27 % and Cmax by 13 %
- decreased the ratio of losartan metabolite E3174 to losartan (CYP2C9 substrate) concentrations in urine by 28%

- did not change the ratio of dextromethorphan metabolite (dextrorphan) to dextromethorphan (CYP2D6 substrate) concentrations in urine.

These results indicate strong induction of CYP3A4, mild inhibition of CYP1A2 and CYP2C9 and no impact on pharmacokinetics of CYP2C19 and CYP2D6 substrates.

A single dose of encorafenib 450 mg and binimetinib 45 mg reduced bupropion 75 mg (CYP2B6 substrate) AUC and Cmax by ≤ 25% and repeated administration of encorafenib 450 mg daily and binimetinib 45 mg twice daily reduced bupropion AUC and Cmax by ≤ 26 % indicating a lack of moderate or strong inhibition or induction.

For UGT1A1 substrates that undergo gut extraction, a minor to moderate interaction with encorafenib is expected.

Use caution when co-administering encorafenib with agents that are substrates of CYP3A4 (e.g. hormonal contraceptives) as it may result in loss of efficacy of those agents. If the coadministration of narrow therapeutic index CYP3A4 substrates cannot be avoided, adjust the dose of these substrates in accordance with their approved Product Information. Use caution when co-administering encorafenib with agents that are substrates of UGT1A1 as it may result in increased toxicity of those agents. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction. Co-administration of encorafenib with binimetinib does not affect binimetinib exposure.

Transporter substrates

Encorafenib is an inhibitor of OATP1B1, OATP1B3 and/or BCRP. 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, OAPTP1B3 and/or BCRP transporters. Coadministration of encorafenib with OATP1B1, OATP1B3 and/or BCRP substrates (such as rosuvastatin, atorvastatin, methotrexate) can result in increased concentrations.

In vitro, encorafenib potentially inhibits a number of other transporters at the expected clinical concentrations. Agents that are substrates of renal transporters OCT2, OAT1, OAT3 (such as furosemide, penicillin) or agents that are substrates of 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 (OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, BCRP and P-gp) should be co-administered with caution.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of encorafenib on fertility in humans. Fertility studies were not conducted with encorafenib. In the sub-acute 28-day and subchronic 13- week rat toxicology studies, encorafenib treatment at 20 mg/kg/day (similar to the human exposure at 450 mg daily

based on unbound AUC) 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/day).

Based on findings in male rats, the use of encorafenib may affect fertility in males of reproductive potential. As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis.

Women of childbearing potential
Women of childbearing potential should be advised to use effective contraception during treatment with encorafenib and for at least 1 month after the last dose. Encorafenib may decrease the efficacy of hormonal contraceptives (see section 4.5 *Interactions with other medicines and other forms of interactions*). Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment with encorafenib and for at least 1 month following the last dose.

Use in pregnancy
Category D.

There are no data on the use of encorafenib in pregnant women. However, studies in animals have demonstrated reproductive toxicity. The embryo-foetal development study in rats indicated that encorafenib induced foetal toxicity with lower foetal weights and delays in skeletal development (incomplete ossification of the bones of the skull and thoracic vertebra) at 20 mg/kg/day (2 times the human exposure at 450 mg daily based on unbound AUC). The embryo-foetal development study in rabbits indicated that encorafenib induced maternal toxicity and foetal toxicity with lower foetal weights, delays in skeletal development (incomplete ossification of the bones of the skull and thoracic vertebra) and visceral malformations (dilation of the aortic arch and ascending aorta, misshapen globular hearts, cardiac interventricular septal defects, small lung lobes and asplenia) at 75 mg/kg/day (14 times the human exposure at 450 mg daily based on total AUC) and delayed ossification (thoracic vertebra) at 25 mg/kg/day (7 times the human exposure).

Encorafenib should not be administered during pregnancy unless the benefits for the mother outweigh the risks for the foetus. 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.

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

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

Melanoma studies

Encorafenib 450 mg once daily with binimetinib 45 mg twice daily

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), who received this regimen across two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, the "COLUMBUS" study; see section 5.1 *Pharmacodynamic properties, Clinical trials*). In the pooled Combo 450 population (n=274), 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 increase and myopathy/muscular disorders.

Encorafenib 300 mg once daily with binimetinib 45 mg twice daily

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) who received this regimen in Part 2 of the COLUMBUS study. The most common adverse reactions (≥ 25%) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea.

Encorafenib 300 mg once daily as a single agent

The safety profile of encorafenib as a single agent (at a dose of 300 mg once daily) is based on data from three clinical studies (Columbus Part 1, CLGX818X2102 and CLGX818X2101) that included 217 patients with unresectable or metastatic BRAF V600-mutant melanoma (hereafter referred to as the pooled encorafenib 300 mg population). The most common adverse drug reactions (ADRs) (≥ 25%) reported with encorafenib monotherapy at this dose were hyperkeratosis, alopecia, PPES fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus.

Non-small cell lung cancer studies

Encorafenib 450 mg once daily with binimetinib 45 mg twice daily

The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 98 patients with BRAF V600E mutant metastatic Non-small cell lung cancer (NSCLC) who received this regimen in the open-label, single-arm trial ARRAY-818-202 "PHAROS" (see section 5.1 *Pharmacodynamic properties, Clinical trials*). The most common ADRs (>25%) reported in this population were: fatigue, nausea, diarrhoea, vomiting, anaemia, abdominal pain, visual impairment, myopathy/muscular disorders and constipation.

Colorectal cancer studies

Encorafenib 300 mg once daily with cetuximab

The safety of encorafenib (300 mg orally once daily) in combination with cetuximab (dosed as per its PI) was evaluated in 216 patients with BRAF V600E-mutant metastatic colorectal cancer who received this regimen in the phase III study ARRAY-818-302 "BEACON CRC" (see section 5.1 *Pharmacodynamic properties, Clinical trials*). 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.

Tabulated summary of adverse reactions

Melanoma studies

Adverse reactions that occurred in patients with melanoma in the Combo 450 population (n=274) and in the pooled encorafenib 300 mg population (n=217) are listed in Table 4, by MedDRA body system organ class (SOC).

Table 4: Adverse reactions occurring in patients with melanoma who received encorafenib 300 mg as monotherapy, or encorafenib 450 mg in combination with binimetinib

	Pooled encorafenib 300 mg population [encorafenib 300 mg monotherapy] (n=217)		**Combo 450 population [encorafenib 450 mg in combination with binimetinib] (n=274)**	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Neoplasms benign, malignant and unspecified				
Skin papilloma*	25 (11.5)	0	22 (8.0)	0
Melanocytic naevus	23 (10.6)	0	4 (1.5)	0
CuSCC[a]	16 (7.4)	0	9 (3.3)	1 (0.4)
Basal cell carcinoma*	2 (0.9)	1 (0.5)	3 (1.1)	0
New primary melanoma*	9 (4.1)	2 (0.9)	1 (0.4)	1 (0.4)
Blood and lymphatic system disorders				
Anaemia	16 (7.4)	5 (2.3)	54 (19.7)	13 (4.7)
Immune system disorders				
Hypersensitivity[b]	8 (3.7)	1 (0.5)	9 (3.3)	0
Metabolism and nutrition disorders				
Decreased appetite	48 (22.1)	1 (0.5)	21 (7.7)	0
Tumour lysis syndrome**	/	/	Not known	Not known

	Pooled encorafenib 300 mg population [encorafenib 300 mg monotherapy] (n=217)		Combo 450 population [encorafenib 450 mg in combination with binimetinib] (n=274)	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Psychiatric disorders				
Insomnia	48 (22.1)	6 (2.8)	23 (8.4)	0
Nervous system disorders				
Headache*	64 (29.5)	7 (3.2)	59 (21.5)	4 (1.5)
Neuropathy peripheral[*]	49 (22.6)	4 (1.8)	36 (13.1)	3 (1.1)
Dysgeusia*	30 (13.8)	0	18 (6.6)	0
Dizziness[*]	15 (6.9)	1 (0.5)	42 (15.3)	7 (2.6)
Facial paresis[c]	16 (7.4)	3 (1.4)	2 (0.7)	1 (0.4)
Eye disorders				
Visual impairment[*]	12 (5.5)	0	59 (21.5)	1 (0.4)
RPED [*]	5 (2.3)	0	81 (29.6)	5 (1.8)
Uveitis[*]	1 (0.5)	0	12 (4.4)	1 (0.4)
Cardiac disorders				
Supraventricular tachycardia [d]	9 (4.1)	2 (0.9)	5 (1.8)	0
LVD[h]	4 (1.8)	2 (0.9)	23 (8.4)	3 (1.1)
Vascular disorders				
Haemorrhage[i]	25 (11.5)	5 (2.3)	49 (17.9)	9 (3.3)
Hypertension [*]	11 (5.1)	6 (2.8)	32 (11.7)	15 (5.5)
VTE [j]	6 (2.8)	2 (0.9)	13 (4.7)	3 (1.1)
Gastrointestinal disorders				
Nausea	82 (37.8)	8 (3.7)	114 (41.6)	7 (2.6)
Vomiting*	60 (27.6)	9 (4.1)	77 (28.1)	6 (2.2)
Constipation	37 (17.1)	0	66 (24.1)	0
Abdominal pain*	34 (15.7)	6 (2.8)	75 (27.4)	7 (2.6)
Diarrhoea*	27 (12.4)	3 (1.4)	104 (38.0)	9 (3.3)
Colitis [k]	2 (0.9)	0	6 (2.2)	2 (0.7)
Pancreatitis*	1 (0.5)	1 (0.5)	2 (0.7)	2 (0.7)
Skin and subcutaneous tissue disorders				
PPES	112 (51.6)	27 (12.4)	17 (6.2)	0
Hyperkeratosis[*]	127 (58.5)	13 (6.0)	57 (20.8)	1 (0.4)
Rash[*]	94 (43.3)	10 (4.6)	54 (19.7)	2 (0.7)
Dry skin[*]	82 (37.8)	0	40 (14.6)	0
Pruritus[*]	64 (29.5)	1 (0.5)	32 (11.7)	1 (0.4)
Alopecia*	124 (57.1)	0	40 (14.6)	0
Erythema [e]	37 (17.1)	3 (1.4)	22 (8.0)	0
Skin hyperpigmentation*	22 (10.1)	0	5 (1.8)	0
Dermatitis acneiform*	17 (7.8)	[0]	12 (4.4)	0
Skin exfoliation [f]	14 (6.5)	1 (0.5)	3 (1.1)	0
Photosensitivity[*]	9 (4.1)	0	11 (4.0)	1 (0.4)
Panniculitis*	1 (0.5)	0	4 (1.5)	0
Musculoskeletal and connective tissue disorders				
Arthralgia*	94 (43.3)	20 (9.2)	74 (27.0)	2 (0.7)
Myalgia [g]	78 (35.9)	20 (9.2)		

	Pooled encorafenib 300 mg population [encorafenib 300 mg monotherapy] (n=217)		Combo 450 population [encorafenib 450 mg in combination with binimetinib] (n=274)	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Myopathy/Muscular disorders[l]			71 (25.9)	2 (0.7)
Pain in extremity	46 (21.2)	2 (0.9)	41 (11.0)	6 (1.6)
Back pain*	33 (15.2)	5 (2.3)	50 (13.4)	3 (0.8)
Arthritis *	11 (5.1)	3 (1.4)	7 (1.9)	0
Rhabdomyolysis	0	0	1 (0.3)	1 (0.3)
Renal and urinary disorders				
Renal failure *	6 (2.8)	3 (1.4)	13 (3.5)	7 (1.9)
General disorders and administration site conditions				
Fatigue*	95 (43.8)	10 (4.6)	179 (48.1)	16 (4.3)
Pyrexia*	33 (15.2)	2 (0.9)	69 (18.5)	8 (2.9)
Peripheral oedema[m]	22 (10.1)	0	42 (15.3)	3 (1.1)
Investigations				
Blood CK increased	2 (0.9)	0	74 (27.0)	16 (5.8)
Gamma-glutamyl transferase (GGT) increased*	25 (11.5)	11 (5.1)	40 (14.6)	23 (8.4)
Transaminase increased*	14 (6.5)	3 (1.4)	43 (15.7)	15 (5.5)
Blood alkaline phosphatase increased	6 (2.8)	0	20 (7.3)	2 (0.7)
Blood creatinine increased*	5 (2.3)	0	17 (6.2)	2 (0.7)
Amylase increased	1(0.5)	0	9 (3.3)	4 (1.5)
Lipase increased	5 (2.3)	3 (1.4)	14 (5.1)	7 (2.6)

*composite terms which included more than one preferred term
**Frequency cannot be estimated from the available data
[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

Non-small cell lung cancer studies

Adverse reactions that occurred in patients with NSCLC (n=98) are listed in Table 5, by MedDRA body system organ class (SOC)**:**

Table 5: Adverse reactions occurring in patients with NSCLC who received encorafenib 450 mg QD in combination with binimetinib (n=98)

Adverse drug reactions	All grades n (%)	Grade 3/4 n (%)
Blood and Lymphatic System Disorders		
Anaemia	32 (32.7)	13 (13.3)

Adverse drug reactions	All grades n (%)	Grade 3/4 n (%)
Cardiac Disorders		
Left ventricular dysfunction (Cardiomyopathy)[a]	12 (12.2)	2 (2.0)
Eye Disorders		
Visual impairment*	27 (27.6)	2 (2.0)
RPED*	2 (2.0)	0
Uveitis*	1 (1.0)	0
Gastrointestinal Disorders		
Nausea	57 (58.2)	4 (4.1)
Diarrhoea	51 (52.0)	5 (5.1)
Vomiting*	39 (39.8)	1 (1.0)
Abdominal pain*	31 (31.6)	1 (1.0)
Constipation	26 (26.5)	0
Colitis[b]	6 (6.1)	3 (3.1)
Pancreatitis*	1 (1.0)	1 (1.0)
Metabolism and nutrition disorders		
Tumour lysis syndrome***	Not known	Not known
General Disorders and Administration Site Conditions		
Fatigue*	59 (60.2)	8 (8.2)
Pyrexia*	22 (22.4)	0
Peripheral oedema[c]	22 (22.4)	1 (1.0)
Immune System Disorders		
Drug hypersensitivity[d]	1 (1.0)	0
Investigations		
Blood CK increased	15 (15.3)	3 (3.1)
Transaminases increased	17 (17.3)	9 (9.2)
GGT increased*	2 (2.0)	2 (2.0)
Blood creatinine increased*	16 (16.3)	0
Blood alkaline phosphatase increased	11 (11.2)	2 (2.0)
Lipase increased	15 (15.3)	9 (9.2)
Amylase increased	6 (6.1)	1 (1.0)
Musculoskeletal and Connective Tissue Disorders		
Myopathy / muscular disorders[e]	26 (26.5)	3 (3.1)
Arthralgia*	16 (16.3)	1 (1.0)
Back pain*	20 (20.4)	1 (1.0)
Pain in extremity	12 (12.2)	2 (2.0)
Neoplasms benign, malignant and unspecified		

Adverse drug reactions	All grades n (%)	Grade 3/4 n (%)
Skin papilloma*	2 (2.0)	0
CuSCC[f]	2 (2.0)	1 (1.0)
Nervous System Disorders		
Headache*	11 (11.2)	0
Dizziness*	19 (19.4)	0
Neuropathy*	10 (10.2)	1 (1.0)
Dysgeusia*	8 (8.2)	0
Facial paresis[g]	1 (1.0)	0
Renal and urinary disorders		
Renal failure*	4 (4.1)	0
Skin and Subcutaneous Tissue Disorders		
Rash*	21 (21.4)	2 (2.0)
Hyperkeratosis*	5 (5.1)	0
Dry skin*	16 (16.3)	0
Alopecia*	12 (12.2)	0
Pruritus*	16 (16.3)	0
Erythema*	2 (2.0)	0
PPES	2 (2.0)	0
Photosensitivity*	3 (3.1)	0
Acneiform dermatitis*	3 (3.1)	1 (1.0)
Vascular Disorders		
Haemorrhage[h] **	13 (13.3)	4 (4.1)
Hypertension*	9 (9.2)	4 (4.1)
VTE[i]	5 (5.1)	0

*composite terms which included more than one preferred term
**Including one (1.0%) Grade 5 adverse reaction of haemorrhage.
***Frequency cannot be estimated from the available data
[a] includes cardiac failure, ejection fraction decreased, left ventricular dysfunction
[b] includes colitis, colitis ulcerative, enterocolitis, proctitis
[c] includes fluid retention generalised oedema localised oedema oedema oedema peripheral peripheral swelling swelling
[d] includes angioedema, drug hypersensitivity, hypersensitivity, vasculitis urticaria
[e] includes muscle spasms, muscular weakness, myalgia, myositis
[f] includes keratoacanthoma, squamous cell carcinoma, squamous cell carcinoma of skin
[g] includes bell's palsy, Facial paralysis, Facial paresis
[h] includes haemorrhage at various sites including cerebral haemorrhage
[i] includes deep vein thrombosis Embolism mesenteric vein thrombosis phlebitis, pulmonary embolism superficial vein thrombosis superior vena cava syndrome thrombophlebitis thrombosis, vena cava thrombosis

Colorectal cancer studies

Adverse reactions in patients who received encorafenib 300 mg in combination with cetuximab in the BEACON CRC study (n=216) are listed in Table 6, by MedDRA body system organ class (SOC).

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.

Table 6: Adverse reactions occurring in patients with colorectal cancer receiving encorafenib in combination with cetuximab at the recommended doses

	Encorafenib 300 mg in combination with cetuximab (n=216)	
	All grades n (%)	**Grade 3/4 n (%)**
Neoplasms benign, malignant and unspecified		
Melanocytic naevus	34 (15.7)	0
cuSCC[a]	3 (1.4)	0
Skin papilloma*	15 (6.9)	0
New primary melanoma[*]	4 (1.9)	2 (0.9)
Basal cell carcinoma	1 (0.5)	0
Immune system disorders		
Hypersensitivity[b]	4 (1.9)	3 (1.4)
Metabolism and nutrition disorders		
Decreased appetite	67 (31.0)	3 (1.4)
Psychiatric disorders		
Insomnia	29 (13.4)	0
Nervous system disorders		
Neuropathy peripheral[*]	32 (14.8)	4 (1.9)
Headache[*]	44 (20.4)	0
Dizziness[*]	20 (9.3)	0
Dysgeusia	10 (4.6)	0
Cardiac disorders		
Supraventricular tachycardia[c]	10 (4.6)	3 (1.4)
Vascular disorders		
Haemorrhage[d]	46 (21.3)	4 (1.9)
Gastrointestinal disorders		
Nausea	82 (38.0)	1 (0.5)
Vomiting	59 (27.3)	3 (1.4)
Constipation	39 (18.1)	0
Abdominal pain[*]	79 (36.6)	11 (5.1)
Diarrhoea[*]	83 (38.4)	6 (2.8)
Pancreatitis[*]	1 (0.5)	1 (0.5)
Skin and subcutaneous tissue disorders		
Dermatitis acneiform[*]	72 (33.3)	2 (0.9)
Rash[*]	66 (30.6)	1 (0.5)
Dry skin[*]	33 (15.3)	0
Pruritus[*]	33 (15.3)	0
Skin hyperpigmentation	16 (7.4)	0
PPES	11 (5.1)	1 (0.5)
Hyperkeratosis*	12 (5.6)	0

	Encorafenib 300 mg in combination with cetuximab (n=216)	
Alopecia	9 (4.2)	0
Erythema[e]	13 (6.0)	1 (0.5)
Skin exfoliation[f]	1 (0.5)	0
Musculoskeletal and connective tissue disorders		
Arthralgia/Musculoskeletal pain*	68 (31.5)	3 (1.4)
Myopathy/Muscular disorder*	38 (17.6)	1 (0.5)
Back pain	28 (13.0)	3 (1.4)
Pain in extremity	25 (11.6)	0
Renal and urinary disorders		
Renal failure*	5 (2.3)	5 (2.3)
General disorders and administration site conditions		
Fatigue*	123 (56.9)	17 (7.9)
Pyrexia*	41 (19.0)	4 (1.9)
Investigations		
Blood creatinine increased*	6 (2.8)	1 (0.5)
Transaminase increased*	19 (8.8)	3 (1.4)
Amylase increased	1 (0.5)	0
Lipase increased	1 (0.5)	1 (0.5)

*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 extrasystoles, sinus tachycardia, supraventricular extrasystoles, tachyarrhythmia, tachycardia
[d] includes haemorrhage at various sites including cerebral haemorrhage
[e] includes erythema, generalised erythema, plantar erythema
[f] includes dermatitis exfoliative, skin exfoliation, exfoliative rash

Adverse events

Adverse events in the COLUMBUS study (melanoma)

Table 7 summarises the most common treatment-emergent adverse events (AEs) (≥ 10% any grade or ≥ 2% grade 3 or 4) occurring in patients in Part I of the phase III randomised, active-controlled, open-label, multicentre trial (COLUMBUS) in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma. The COLUMBUS study excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion.

In Part 1 of the COLUMBUS study, serious adverse events (SAEs) regardless of relationship to study therapy were reported in 35.9% of patients with melanoma treated with encorafenib

450 mg in combination with binimetinib (Combo 450), 34.9% of patients treated with encorafenib single agent 300 mg (Enco 300) and in 38.2% of patients treated with vemurafenib.

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

Table 7: Treatment-emergent adverse events occurring very commonly (≥ 10% any grade or ≥ 2 % grades 3 or 4) inpatients receiving Combo 450 mg, Enco 300 mg or vemurafenib in Part 1 of the COLUMBUS study

	Combo 450 N=192 n (%)		**Enco 300 N=192 n (%)**		**Vemurafenib N=186 n (%)**	
Grade	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	189 (98.4)	115 (59.9)	191 (99.5)	128 (66.7)	186 (100.0)	118 (63.4)
Nausea	83 (43.2)	3 (1.6)	74 (38.5)	8 (4.2)	65 (34.9)	3 (1.6)
Diarrhoea	71 (37.0)	5 (2.6)	26 (13.5)	3 (1.6)	64 (34.4)	4 (2.2)
Vomiting	58 (30.2)	3 (1.6)	54 (28.1)	9 (4.7)	29 (15.6)	2 (1.1)
Fatigue	56 (29.2)	4 (2.1)	48 (25.0)	1 (0.5)	57 (30.6)	4 (2.2)
Arthralgia	51 (26.6)	1 (0.5)	84 (43.8)	18 (9.4)	83 (44.6)	11 (5.9)
Blood CK increased	44 (22.9)	13 (6.8)	2 (1.0)	0	4 (2.2)	0
Headache	44 (22.9)	3 (1.6)	53 (27.6)	6 (3.1)	36 (19.4)	1 (0.5)
Constipation	43 (22.4)	0	29 (15.1)	0	12 (6.5)	1 (0.5)
Asthenia	39 (20.3)	3 (1.6)	40 (20.8)	5 (2.6)	35 (18.8)	8 (4.3)
Pyrexia	37 (19.3)	7 (3.6)	30 (15.6)	2 (1.0)	52 (28.0)	0
Abdominal pain	33 (17.2)	5 (2.6)	13 (6.8)	4 (2.1)	13 (7.0)	1 (0.5)
Vision blurred	31 (16.1)	0	4 (2.1)	0	4 (2.2)	0
Anaemia	30 (15.6)	9 (4.7)	12 (6.3)	5 (2.6)	15 (8.1)	5 (2.7)
GGT increased	29 (15.1)	18 (9.4)	23 (12.0)	10 (5.2)	21 (11.3)	6 (3.2)
Dry skin	28 (14.6)	0	58 (30.2)	0	42 (22.6)	0
Hyperkeratosis	28 (14.6)	1 (0.5)	74 (38.5)	7 (3.6)	54 (29.0)	0
Myalgia	28 (14.6)	0	55 (28.6)	19 (9.9)	34 (18.3)	1 (0.5)
Rash	28 (14.6)	2 (1.0)	40 (20.8)	4 (2.1)	54 (29.0)	6 (3.2)
Alopecia	27 (14.1)	0	108 (56.3)	0	68 (36.6)	0
Dizziness	27 (14.1)	4 (2.1)	11 (5.7)	0	5 (2.7)	0
Abdominal pain upper	23 (12.0)	2 (1.0)	18 (9.4)	2 (1.0)	17 (9.1)	1 (0.5)
Pruritus	23 (12.0)	1 (0.5)	42 (21.9)	1 (0.5)	20 (10.8)	0
Pain in extremity	22 (11.5)	2 (1.0)	43 (22.4)	2 (1.0)	26 (14.0)	2 (1.1)
ALT increased	21 (10.9)	10 (5.2)	10 (5.2)	2 (1.0)	14 (7.5)	3 (1.6)
Hypertension	21 (10.9)	10 (5.2)	11 (5.7)	6 (3.1)	22 (11.8)	6 (3.2)
Oedema peripheral	21 (10.9)	3 (1.6)	15 (7.8)	0	20 (10.8)	1 (0.5)
Muscle spasms	20 (10.4)	1 (0.5)	6 (3.1)	0	4 (2.2)	0
Nasopharyngitis	20 (10.4)	0	14 (7.3)	0	19 (10.2)	0
Back pain	19 (9.9)	1 (0.5)	29 (15.1)	5 (2.6)	12 (6.5)	3 (1.6)
Insomnia	19 (9.9)	0	35 (18.2)	5 (2.6)	15 (8.1)	0
Palmoplantar keratoderma	18 (9.4)	0	50 (26.0)	3 (1.6)	31 (16.7)	2 (1.1)
AST increased	16 (8.3)	4 (2.1)	8 (4.2)	1 (0.5)	15 (8.1)	3 (1.6)
Decreased appetite	16 (8.3)	0	40 (20.8)	1 (0.5)	36 (19.4)	2 (1.1)

	Combo 450 N=192 n (%)		Enco 300 N=192 n (%)		Vemurafenib N=186 n (%)	
Grade	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Skin papilloma	15 (7.8)	0	19 (9.9)	0	31 (16.7)	0
Erythema	14 (7.3)	0	25 (13.0)	1 (0.5)	31 (16.7)	1 (0.5)
PPES	14 (7.3)	0	98 (51.0)	26 (13.5)	26 (14.0)	2 (1.1)
Musculoskeletal pain	11 (5.7)	0	31 (16.1)	6 (3.1)	11 (5.9)	2 (1.1)
Dysgeusia	10 (5.2)	0	22 (11.5)	0	17 (9.1)	0
Hyperglycaemia	9 (4.7)	4 (2.1)	6 (3.1)	4 (2.1)	0	0
Keratosis pilaris	9 (4.7)	0	33 (17.2)	0	43 (23.1)	0
Photosensitivity reaction	7 (3.6)	1 (0.5)	7 (3.6)	0	46 (24.7)	2 (1.1)
Weight decreased	6 (3.1)	0	29 (15.1)	2 (1.0)	20 (10.8)	0
General physical health deterioration	5 (2.6)	4 (2.1)	4 (2.1)	3 (1.6)	9 (4.8)	8 (4.3)
Keratoacanthoma	5 (2.6)	1 (0.5)	13 (6.8)	0	21 (11.3)	6 (3.2)
Metastases to central nervous system	5 (2.6)	3 (1.6)	5 (2.6)	4 (2.1)	3 (1.6)	3 (1.6)
Pain	4 (2.1)	2 (1.0)	12 (6.3)	7 (3.6)	3 (1.6)	0
Pleural effusion	4 (2.1)	4 (2.1)	3 (1.6)	2 (1.0)	2 (1.1)	1 (0.5)
Pruritus generalised	4 (2.1)	0	18 (9.4)	0	19 (10.2)	2 (1.1)
Rash generalised	4 (2.1)	0	13 (6.8)	1 (0.5)	17 (9.1)	8 (4.3)
Rash maculo-papular	4 (2.1)	0	18 (9.4)	1 (0.5)	27 (14.5)	8 (4.3)
Squamous cell carcinoma	2 (1.0)	0	3 (1.6)	0	12 (6.5)	8 (4.3)
Sunburn	0	0	1 (0.5)	0	19 (10.2)	1 (0.5)

A patient is counted once within each preferred term.
Preferred terms are sorted in descending frequency in the 'Combo 450' column.
MedDRA Version 19.0 has been used for the reporting of adverse events.

Adverse events in the PHAROS study (non-small cell lung cancer)

Table 8 summarises the most common (incidence of at least 10%) treatment-emergent AEs occurring in patients in the PHAROS study. The PHAROS study excluded patients with abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion.

Serious adverse reactions occurred in 43.9% of patients who received encorafenib 450 mg in combination with binimetinib. Permanent discontinuations due to AEs were reported in 17.3% of patients treated. The most frequently reported AEs leading to encorafenib discontinuation (≥ 2 (participants) were diarrhoea, nausea, vomiting and myalgia (2.0% each).

Table 8: Treatment-emergent adverse events occurring very commonly (≥ 10%) in patients receiving encorafenib 450 mg in combination with binimetinib in the PHAROS study (n=98)

	Encorafenib 450 mg plus binimetinib N=98	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**
Any preferred term	97 (99.0)	69 (70.4)
Nausea	57 (58.2)	4 (4.1)
Diarrhoea	51 (52.0)	5 (5.1)
Fatigue	44 (44.9)	4 (4.1)
Vomiting	39 (39.8)	1 (1.0)
Arthralgia	15 (15.3)	1 (1.0)
Constipation	26 (26.5)	0
Blood creatine phosphokinase increased	15 (15.3)	3 (3.1)
Anaemia	32 (32.7)	13 (13.3)
Pyrexia	22 (22.4)	0
Headache	10 (10.2)	0
Abdominal pain	19 (19.4)	1 (1.0)
Vision blurred	20 (20.4)	1 (1.0)
Asthenia	16 (16.3)	4 (4.1)
Oedema peripheral	21 (21.4)	0
Alopecia	12 (12.2)	0
Back pain	20 (20.4)	1 (1.0)
Dry skin	14 (14.3)	0
Myalgia	12 (12.2)	2 (2.0)
Rash	12 (12.2)	1 (1.0)
Alanine aminotransferase increased	13 (13.3)	5 (5.1)
Muscle spasms	12 (12.2)	0
Dyspnoea	26 (26.5)	8 (8.2)
Pruritus	15 (15.3)	0
Cough	16 (16.3)	0
Gamma-glutamyltransferase increased	2 (2.0)	2 (2.0)
Aspartate aminotransferase increased	15 (15.3)	7 (7.1)
Hyperkeratosis	5 (5.1)	0
Pain in extremity	12 (12.2)	2 (2.0)
Hypertension	9 (9.2)	4 (4.1)
Blood creatinine increased	16 (16.3)	0
Decreased appetite	14 (14.3)	1 (1.0)

	Encorafenib 450 mg plus binimetinib N=98	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**
Insomnia	11 (11.2)	0
Blood alkaline phosphatase increased	11 (11.2)	2 (2.0)
Nasopharyngitis	1 (1.0)	0
Lipase increased	15 (15.3)	9 (9.2)
Ejection fraction decreased	10 (10.2)	1 (1.0)
Weight increased	11 (11.2)	1 (1.0)
Hyponatraemia	12 (12.2)	10 (10.2)
Productive cough	11 (11.2)	0
COVID-19	10 (10.2)	0

A patient is counted once within each preferred term.
Preferred terms are sorted in descending frequency.
MedDRA Version 25.1 has been used for the reporting of adverse events.

Adverse events in the BEACON CRC study (colorectal cancer)

Table 9 summarises the most common (incidence of at least 10%) treatment-emergent adverse events (AEs) occurring in patients in the BEACON CRC study. The BEACON CRC study excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (> 480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion.

Serious adverse events (SAEs) regardless of relationship to study therapy were reported in 40% of patients who received encorafenib 300 mg in combination with cetuximab. Adverse events leading to dose interruptions of BRAFTOVI occurred in 39% of patients receiving BRAFTOVI in combination with cetuximab; the most common were vomiting (6%), diarrhoea (4%) nausea (4%), pyrexia (3%), and fatigue (2%), Adverse events leading to dose reductions of BRAFTOVI occurred in 10% of patients receiving BRAFTOVI in combination with cetuximab; the most common were fatigue (1.4%), musculoskeletal pain (1.4%), and peripheral neuropathy (1.4%). Permanent discontinuations due to AEs were reported in 11% of patients who received encorafenib 300 mg in combination with cetuximab. None of the adverse events leading to permanent discontinuation of BRAFTOVI occurred in more than 2patients (0.9%).

Table 9: Treatment-emergent adverse events occurring very commonly (≥ 10%) in patients receiving encorafenib 300 mg in combination with cetuximab in the BEACON CRC study

	Encorafenib plus cetuximab N=216 (%)		**Irinotecan plus cetuximab or FOLFIRI plus cetuximab N=193 (%)**	
Grade	All Grades	Grade 3/4	All Grades	Grade 3/4
Any event	212 (98.1)	124 (57.4)	190 (98.4)	124 (64.2)
Diarrhoea	83 (38.4)	6 (2.8)	94 (48.7)	20 (10.4)
Nausea	82 (38.0)	1 (0.5)	84 (43.5)	3 (1.6)
Fatigue	72 (33.3)	9 (4.2)	54 (28.0)	9 (4.7)
Decreased appetite	67 (31.0)	3 (1.4)	56 (29.0)	6 (3.1)
Dermatitis acneiform	65 (30.1)	1 (0.5)	77 (39.9)	5 (2.6)
Abdominal pain	60 (27.8)	7 (3.2)	54 (28.0)	10 (5.2)
Vomiting	59 (27.3)	3 (1.4)	61 (31.6)	6 (3.1)
Asthenia	52 (24.1)	8 (3.7)	53 (27.5)	10 (5.2)
Arthralgia	49 (22.7)	3 (1.4)	3 (1.6)	0 (0.0)
Headache	43 (19.9)	0 (0.0)	5 (2.6)	0 (0.0)
Anaemia	42 (19.4)	12 (5.6)	36 (18.7)	13 (6.7)
Pyrexia	40 (18.5)	3 (1.4)	28 (14.5)	1 (0.5)
Constipation	39 (18.1)	0 (0.0)	39 (20.2)	2 (1.0)
Melanocytic naevus	34 (15.7)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	33 (15.3)	1 (0.5)	4 (2.1)	0 (0.0)
Rash	32 (14.8)	0 (0.0)	28 (14.5)	3 (1.6)
Musculoskeletal pain	29 (13.4)	0 (0.0)	5 (2.6)	0 (0.0)
Back pain	28 (13.0)	3 (1.4)	27 (14.0)	2 (1.0)
Dyspnoea	28 (13.0)	2 (0.9)	20 (10.4)	6 (3.1)
Dry skin	28 (13.0)	0 (0.0)	16 (8.3)	1 (0.5)
Hypomagnesaemia	25 (11.6)	1 (0.5)	19 (9.8)	3 (1.6)
Pain in extremity	25 (11.6)	0 (0.0)	2 (1.0)	0 (0.0)
Weight decreased	24 (11.1)	1 (0.5)	12 (6.2)	0 (0.0)
Insomnia	24 (11.1)	0 (0.0)	13 (6.7)	0 (0.0)
Pruritus	24 (11.1)	0 (0.0)	10 (5.2)	0 (0.0)
Oedema peripheral	23 (10.6)	0 (0.0)	14 (7.3)	1 (0.5)
Abdominal pain upper	22 (10.2)	2 (0.9)	15 (7.8)	1 (0.5)
Alopecia	22 (10.2)	2 (0.9)	15 (7.8)	1 (0.5)

A patient is counted once within each preferred term.
Preferred terms are sorted in descending frequency in the 'Encorafenib+cetuximab' column.
MedDRA Version 21.0 has been used for the reporting of adverse events.

Description of selected adverse reactions

Cutaneous malignancies

Cutaneous squamous cell carcinoma

Melanoma studies

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 to 22.8 months).

In the pooled encorafenib 300 population, cuSCC was reported in 7.4% (16/217) patients. For patients in the COLUMBUS study 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).

NSCLC studies

In patients treated with Combo 450, cuSCC was observed in 2.0% (2/98) of patients (no keratoacanthoma). The times to first event of cuSCC (all grades) were 6.2 and 7.1 months for these 2 patients.*Colorectal cancer studies*

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 studies

In the pooled encorafenib 300 population, new primary melanoma events occurred in 4.1% of patients (9 /217) and were 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 studies

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 studies

In the pooled Combo 450 population, RPED was reported in 29.6 % (81/274) of patients. RPED was Grade 1 (asymptomatic) in 21.2% (58/274) of patients, Grade 2 in 5.8% (16/274) and Grade 3 in 1.8% (5/274). Most of these events were reported as retinopathy (9.5%, 26/274), retinal detachment (6.6%, 18/274), subretinal fluid (6.2%, 17/274), macular oedema (5.1%, 14/274) and chorioretinopathy (3.3%, 9/274); and led to dose interruptions or dose modifications in 4.7% (13/274) of patients. RPED was generally reversible. The median time to onset of the first event of RPED (all grades) was 1.5 months (0.03 to 17.5 months).

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.

NSCLC studies
In patients treated with Combo 450, RPED was reported in 2% (2/98) of patients (one Grade 1 and one Grade 2). Uveitis was reported in 1% (1/98) of patients (Grade 1). Visual impairment, including blurred vision and reduced visual acuity, occurred in 27.6% (27/98) of patients. Visual impairment was generally reversible.

Left ventricular dysfunction
Melanoma and NSCLC studies
LVD was reported when encorafenib is used in combination with binimetinib in patients with melanoma and NSCLC (see section 4.8 Adverse effects (undesirable effects) of binimetinib PI).

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

In the Combo 300 population of the COLUMBUS study, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3 or 4 in 1.6% (4/257) of patients.

NSCLC studies
Haemorrhagic events have been observed in 13.3% (13/98) of patients with NSCLC treated with Combo 450, including 4.1% of patients with Grade≥3 events. No haemorrhagic events led to discontinuation of treatment in NSCLC population. Dose reduction was required in 5.1% (5/98) of patients. One event of haemorrhage intracranial with fatal outcome (Grade 5) occurred.

Colorectal cancer studies
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.

Hypertension

Melanoma and NSCLC studies

Hypertension was reported when encorafenib was used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 Adverse effects (undesirable effects) of binimetinib PI).

Venous thromboembolism

Melanoma and NSCLC studies

VTE was reported when encorafenib was used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 Adverse effects (undesirable effects) of binimetinib PI).

Pancreatitis

Melanoma studies

In the pooled Combo 450 population, pancreatic enzyme elevation, mostly asymptomatic, was reported. Amylase and lipase elevations have been reported in 3.3% (9/274) and 5.1% (14/274) of patients, respectively. Pancreatitis adverse reactions were 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.

NSCLC studies

Pancreatitis adverse reactions were reported in 1% (1/98) of patients with NSCLC treated with Combo 450 (event of Grade 3). Amylase and lipase elevations have been reported in 6.1% (6/98) and 15% (15/98) of patients, respectively.

Colorectal cancer studies

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%). Pancreatitis recurred on re-challenge twice, despite dose reductions each time, and led to permanent discontinuation.

Dermatological reactions

Rash

Melanoma studies

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

In the pooled encorafenib 300 population, rash was reported in 43.3% (94/217) of patients. Most of the events were mild, with Grade 3 or 4 events reported in 4.6% (10/217) of patients who received encorafenib as a single agent. 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.

NSCLC studies
Rash occurred in 21.4% (21/98) of patients with NSCLC treated with Combo 450 including 2.0% of Grade 3 events.

Colorectal cancer studies
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 studies
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 pooled encorafenib 300 population, PPES was reported in 51.6% (112/217) of patients. Most of the events were mild to 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.

NSCLC studies
PPES was reported in 2% (2/98) of patients in the Combo 450 NSCLC population (one Grade 1 and one Grade 2). One event led to dose interruption or dose modification, none led to discontinuation.

Colorectal cancer studies
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 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.

Dermatitis acneiform
Melanoma and NSCLC studies
Dermatitis acneiform was reported when encorafenib was used in combination with binimetinib (see section 4.8 *Adverse effects (undesirable effects)* of the binimetinib PI).

Colorectal cancer studies
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 studies

In the pooled Combo 450 population, photosensitivity was observed in 4.0% (11/274) of patients. Most events were Grade 1 or 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.

NSCLC studies

Photosensitivity was reported in 3.1% (3/98) of patients in the Combo 450 NSCLC population (two Grade 1 and one Grade 2). None led to dose interruption, modification or discontinuation.

Facial paresis

Melanoma studies

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 to 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.

NSCLC studies

One Grade 1 event of facial paresis was reported in the Combo 450 NSCLC population (1.0% of patients), not leading to dose interruption, modification or discontinuation.

CK elevation / rhabdomyolysis

Melanoma and NSCLC studies

CK elevation and rhabdomyolysis occurred when encorafenib was used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 Adverse Effects (undesirable effects) of binimetinib PI).

Renal dysfunction

Melanoma studies

In the pooled Combo 450 population, mild mostly Grade 1 asymptomatic blood serum creatinine elevation was reported in 6.2% (17/274) of patients. 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) of 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.

NSCLC studies
In the NSCLC population treated with Combo 450, blood creatinine increased was reported in 16.3% (16/98) of patients; all events were of Grade 1 or Grade 2. Renal failure events, all corresponding to acute kidney injury, were reported in 4.1% (4/98) of patients (three Grade 2 and one Grade 3).

Colorectal cancer studies
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.

Liver laboratory abnormalities
Melanoma studies
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 the Combo 300 arm of the COLUMBUS study, the incidence of liver laboratory abnormalities was:

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

NSCLC studies
The incidences of liver laboratory abnormalities reported in the NSCLC population treated with Combo 450 are listed below:

- Increased transaminases: 17.3% (17/98) overall – Grade 3-4: 9.2% (9/98)
- Increased GGT: 2.0% (2/98) overall – Grade 3-4: 2.0% (2/98)

Colorectal cancer studies
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 studies
In the pooled Combo 450 population, diarrhoea was observed in 38% (104/274) of patients and was Grade 3 or 4 in 3.3% (9/274) of patients. Diarrhoea led to dose discontinuation in 0.4% of patients and to dose interruption or dose modification in 4.4% of patients.

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

NSCLC studies
In the NSCLC population treated with Combo 450, diarrhoea was observed in 52% (51/98) of patients and was Grade 3 in 5.1% of patients (no Grade 4). Diarrhoea led to dose discontinuation in 2.0% of patients and to dose interruption or dose modification in 18.4% of patients. Constipation occurred in 26.5% (26/98) of patients and was Grade 1 or 2. Abdominal pain was reported in 31.6% (31/98) of patients and was Grade 3 in 1.0% of patients. Nausea occurred in 58.2% (57/98) with Grade 3 observed in 4.1% of patients. Vomiting occurred in 39.8% (39/98) of patients and was Grade 3 in 1.0% of patients.

Colorectal cancer studies
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.

Anaemia
Melanoma studies
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 the Combo 300 population of

the COLUMBUS study, anaemia was observed in 9.7% (25/257) of patients with Grade 3 or 4 reported in 2.7% (7/257) of patients.

NSCLC studies

In the NSCLC population treated with Combo 450, anaemia was reported in 32.7% (32/98) of patients including 13.3% of patients with Grade 3 (no Grade 4). No patients discontinued treatment due to anaemia, 7.1% required dose interruption or dose modification.

Headache

Melanoma studies

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

NSCLC studies

In the NSCLC population treated with Combo 450, headache was reported in 11.2% (11/98) of patients (only Grade 1 and Grade 2). None led to dose interruption, modification or discontinuation.

Colorectal cancer studies

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 studies

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

NSCLC studies

In the NSCLC population treated with Combo 450, Fatigue was observed in 60.2% (59/98) of patients and was Grade 3 in 8.2% of patients (no Grade 4). Fatigue led to dose discontinuation in 2.0% of patients and to dose interruption or dose modification in 11.2% of patients.

Colorectal cancer studies

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 patients

The number of patients aged 75 years or older enrolled in clinical studies was not sufficient to enable meaningful assessment of differential safety in this population compared to younger patients, in any tumour type.

Melanoma studies

In patients treated with Combo 450 (n=274), 194 patients (70.8%) were < 65 years, 65 patients (23.7%) were 65 to 74 years and 15 patients (5.5%) were aged > 75. No overall differences in safety or efficacy were observed between elderly patients (≥ 65) and younger patients. Patients aged ≥ 65 years did not experience more frequent adverse reactions than younger patients.

NSCLC studies

In the NSCLC population treated with Combo 450, 36 (36.7%) participants were aged < 65 years and 62 (63.2%) participants were aged ≥ 65 years, including 20.4% aged ≥ 75 years. No notable differences in safety profile were observed between elderly patients (≥ 65) and younger patients.

The most common adverse reactions reported with a higher incidence in patients aged ≥ 75 years compared to patients aged < 75 years included diarrhoea, fatigue and nausea (70.0% each), vomiting (55.0%) and blood creatinine increased (25.0%).

Colorectal cancer studies

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 adverse reactions reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included fatigue, decreased appetite and haemorrhage..

In the colorectal cancer population, differences in the incidence of adverse reactions for patients treated in the age subgroup of patients aged ≥ 75 years (n=20), compared to patients aged < 75 years could not be assessed due to the small numbers in the older age range.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems

4.9. OVERDOSE

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). AEs reported by this patient were Grade 1 events of nausea, vomiting and blurred vision; all were subsequently resolved.

Management of overdose
There is no specific treatment for overdose with encorafenib. If overdose occurs, 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. Since encorafenib is moderately bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with encorafenib.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action
Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor.
ATC code: L01EC03

Encorafenib is an ATP-competitive small molecule RAF kinase inhibitor. The 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, V600D and V600K). However, it does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF. Encorafenib also binds to other kinases in vitro including STK36, JNK1/2/3, LIMK1/2 and MEK4/5, at clinically achievable concentrations. Specifically, encorafenib inhibits *in vitro* and *in vivo* BRAF V600E, V600D and V600K mutation-positive melanoma cell growth and BRAF V600E mutant colorectal cancer cell growth. *In vivo*, encorafenib has been evaluated for its ability to inhibit pERK and pMEK, and tumour growth in xenograft models in nude mice. Overall, encorafenib has demonstrated potent activity against RAF enzymes and possesses anti-proliferative activity *in vitro* and *in vivo* in BRAF mutant tumour xenograft models.

Combination with binimetinib
In non-clinical studies, the combination of encorafenib and binimetinib demonstrated additive or synergistic anti-proliferative activity *in vitro* in numerous BRAF-mutant cell lines. *In vivo*, treatment with the combination resulted in greater anti-tumour activity with respect to tumour growth inhibition and better tumour responses (PR and SD) in BRAF V600E mutant human melanoma xenograft studies in mice than that which was achieved with either agent alone.

Combination with cetuximab
One of the main mechanisms of resistance of BRAF-mutant mCRC 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) with agents targeting EGFR (e.g. cetuximab) have been shown to improve anti-tumour efficacy in non-clinical models.

Clinical trials

COLUMBUS - BRAF V600 mutant unresectable or metastatic melanoma

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

In Part 1 of the study, patients were randomised to receive encorafenib 450 mg orally once daily and binimetinib 45 mg orally twice daily (Combo 450, N=192), encorafenib 300 mg orally once daily (Enco 300, N=194), or vemurafenib 960 mg orally twice daily (Vem, N=191). In Part 2, patients were randomised to receive encorafenib 300 mg orally once daily and binimetinib 45 mg orally twice daily (Combo 300, N=258) or encorafenib 300 mg orally once daily (n=86). Safety data from Part 2 are reflected in section 4.8 *Adverse effects (undesirable effects)*. Treatment continued until disease progression or unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1) and prior immunotherapy for unresectable or metastatic disease (yes versus no).

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

The median age for patients was 56 years (range 20 to 89), 58% were male, 90% were Caucasian, and 72% of patients had baseline ECOG performance status of 0.

Most patients had metastatic disease (95%) and were Stage IVM1c (64%); 27% of patients had elevated baseline serum LDH, and 45% of patients had ≥ 3 organs with tumour involvement at baseline and 3.5% had brain metastases.

A total of 27 patients (5%) had received prior checkpoint inhibitors (anti-PD1/PDL1 or ipilimumab) (8 patients in Combo 450 arm, 4%; 7 patients in vemurafenib arm, 4%; 12 patients in Enco 300 arm(6%) including 22 patients in the metastatic setting (6 patients in Combo 450 arm; 5 patients in vemurafenib arm; 11 patients in Enco 300 arm) and 5 patients in the adjuvant setting (2 patients in Combo 450 arm; 2 patients in vemurafenib arm; 1 patient in Enco 300

arm).Most patients were BRAF V600E mutant (88.6%), while the remainder were V600K mutant (10.9%).

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

The COLUMBUS study demonstrated a statistically significant improvement in PFS in patients treated with Combo 450 compared with patients treated with vemurafenib. Patients treated with Combo 450 also had improved ORR, DCR, and DoR compared with patients treated with vemurafenib. Table 8 and Figure 1 summarise the PFS and other efficacy results based on central review of the data by the BIRC (Blinded Independent Radiology Committee).

Table 10: Progression-free survival and confirmed overall response results (cut-off date: 19 May 2016, independent central review)

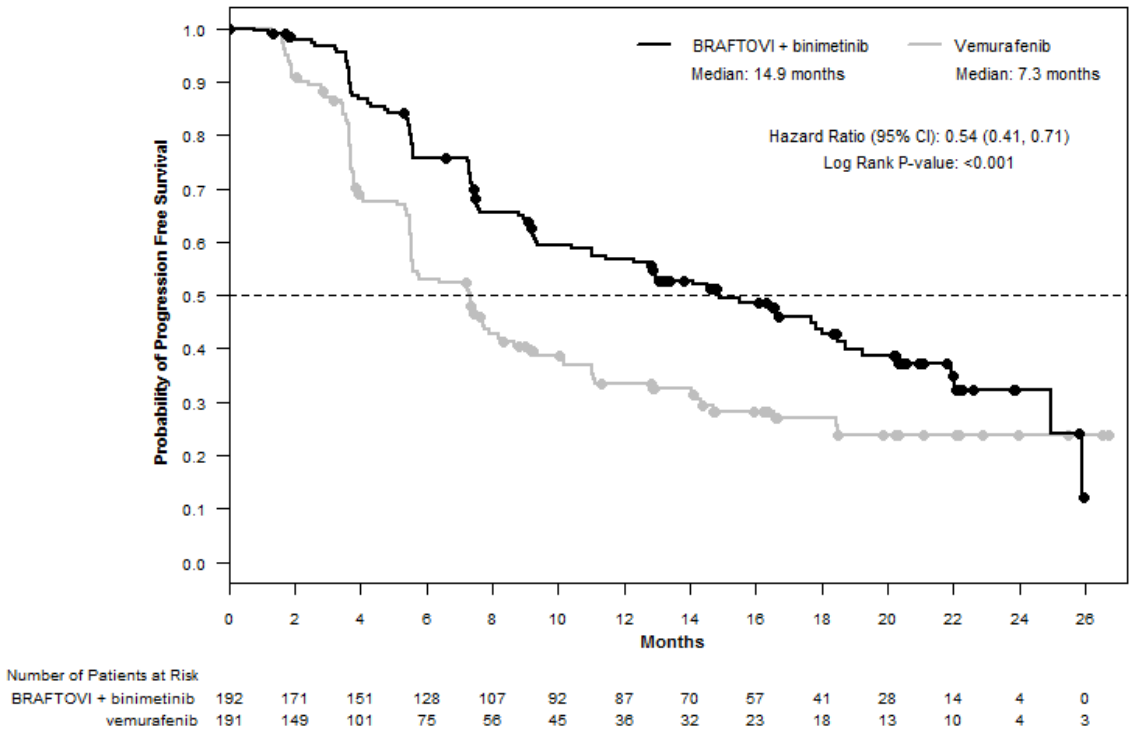
	Combo 450 Encorafenib and binimetinib N = 192	**Enco 300 Encorafenib N = 194**	**Vem N = 191**
Progression Free Survival			
Number of progressive disease (PD) events (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	7.3 (5.6, 8.2)
HR[a] (95% CI) (vs. Vem) P-value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

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

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

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

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



The efficacy results based on investigator assessment were consistent with the independent central assessment The PFS analysis per investigator assessment showed an improvement of PFS in patients treated with Combo 450 compared with patients treated with vemurafenib (14.8 vs 7.3 months, respectively), HR 0.49 (95 % CI 0.37, 0.64) ($p < 0.001$ one sided).
The ORR analysis per investigator assessment showed an improvement of ORR in patients treated with Combo 450 compared with patients treated with vemurafenib: (75% (95 % CI 68.3, 81.0) vs 49.2 % (95% CI 41.9 56.5), respectively ($p < 0.001$ one sided). In the Combo 450 arm, CR was 16.1%, PR 58.9 % and SD 18.2%.

At a cut-off date of 7 November 2017, an update of the PFS analyses was performed. The PFS analysis per independent central review showed an improvement of PFS in patients treated with Combo 450 compared with patients treated with vemurafenib (14.9 vs 7.3 months, respectively), HR 0.51 (95 % CI 0.39, 0.67) ($p < 0.001$ one sided) and also compared with patients treated with encorafenib (14.9 vs 9.6 months, respectively), HR 0.77 (95 % CI 0.59, 1.0) ($p = 0.0249$ one sided). The analysis per central review showed that encorafenib improved PFS vs. vemurafenib (9.6 vs 7.3 months, respectively), HR 0.68 (95 % CI 0.52, 0.88) ($p = 0.0019$ one sided). The PFS results per investigator review showed consistent results.

An interim OS analysis of Part 1 of the COLUMBUS study, performed at the cut-off date of 7 November 2017, demonstrated a statistically significant improvement in OS for Combo 450 compared with vemurafenib (HR 0.61, 95% CI 0.47, 0.79). See Table 9 and Figure 2.

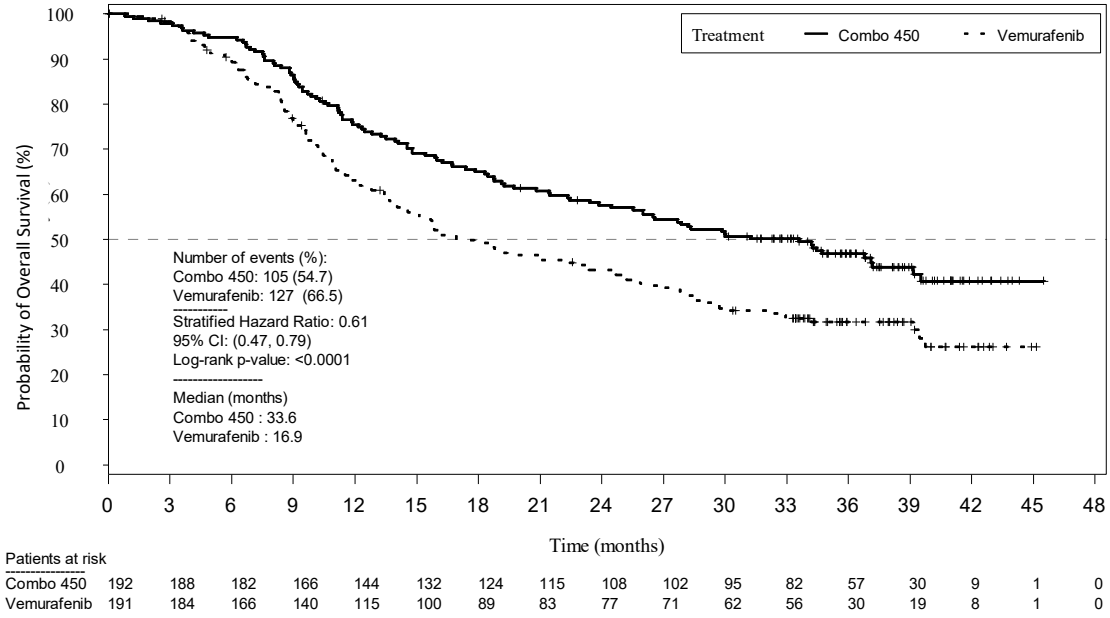
A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4% Combo 450 arm, 36.1% Enco 300 arm, 39.8% vemurafenib arm).

Table 11: Overall survival interim results (cut-off date: 7 November 2017)

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

CI = confidence interval; HR = hazard ratio.

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



Subgroup analyses of PFS

All subgroup analyses of PFS per BIRC including gender, age (< 65/≥ 65), region (North America, Europe, Australia, other), number of organs involved at baseline (1, 2, 3, > 3), LDH at baseline (< ULN/≥ ULN), ECOG performance status (0/1), AJCC Stage (IIIB, IIIC, IVM1a, IVM1b/IVM1c), and prior adjuvant therapy (Yes/No) demonstrated point estimates in favour

of the Combo 450 arm, except for the presence of brain metastases at baseline, a subgroup that only included 12 patients. Most of the HRs in the Combo 450 arm relative to the vemurafenib arm were within the range of the HR observed in the overall population.

Quality of Life (QoL) (Cut-off date: 19 May 2016)
The Functional Assessment of Cancer Therapy-Melanoma (FACT-M), the European 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 side effects. The data showed favourable outcomes for the Combo 450 arm over the vemurafenib arm. The median time to definitive 10% deterioration in the FACT-M score was not reached in the Combo 450 arm and was 22.1 months (95% CI 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI 0.29, 0.72). The median time to definitive 10% deterioration in the EORTC QLQ-C30 global health status score was delayed by more than 7 months in the Combo 450 arm compared to the vemurafenib arm: 23.9 months (95% CI 20.4, NE) vs. 16.6 months (95% CI 11.9, NE) with a HR for the difference of 0.55 (95% CI 0.37, 0.80). As these were exploratory endpoints, they must be interpreted with caution in the context of an open-label study design.

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 (p-values < 0.001).

Cardiac electrophysiology
In a pooled safety analysis across melanoma studies, the incidence of new QTcF prolongation >500 ms was 0.7% (2/268) in the Combo 450 population, and 2.5% (5/203) in the pooled encorafenib 300 mg population. QTcF prolongation of > 60 ms compared to pre-treatment values was observed in 4.9% (13/268) patients in the Combo 450 population, and in 3.4% (7/204) in the pooled encorafenib 300 mg population (see Sections 4.2 *Dose and method of administration* and 4.4 *Special warnings and special precautions for use)*.

<u>BEACON CRC - BRAF V600E mutant metastatic colorectal cancer (mCRC)</u>
Encorafenib in combination with cetuximab was evaluated in BEACON CRC: a randomised, active-controlled, open-label, multicentre trial (also known as ARRAY 818-302). Eligible patients were required to have metastatic colorectal cancer harbouring a BRAF V600E mutation (as detected using the Qiagen therascreen BRAF V600E RGQ polymerase chain reaction (PCR) Kit) that had progressed after 1 or 2 prior regimens. Other key eligibility criteria included absence of prior treatment with a RAF, MEK, or EGFR inhibitor, eligibility to receive cetuximab per local labelling with respect to tumour RAS status, and ECOG performance status (PS) 0-1. Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), prior use of irinotecan (yes versus no), and cetuximab product used (US-licensed versus EU-approved).

A total of 665 patients were randomised (1:1:1) to one of the following treatment arms:

- Encorafenib 300 mg orally once daily in combination with cetuximab (encorafenib plus cetuximab arm) [n=220]
- Encorafenib 300 mg orally once daily in combination with binimetinib and cetuximab [n=224]
- Irinotecan with cetuximab or irinotecan/5-fluorouracil/folinic acid (FOLFIRI) with cetuximab (control arm) [n=221]

Cetuximab was dosed as per its approved European label (SmPC). Patients in the control arm received cetuximab with either irinotecan 180 mg/m2 intravenously on Days 1 and 15 of each 28-day cycle or FOLFIRI intravenously (irinotecan 180 mg/m2 on Days 1 and 15; folinic acid 400 mg/m2 on Days 1 and 15; then fluorouracil 400 mg/m2 bolus on Days 1 and 15 followed by fluorouracil 2400 mg/m2/day by continuous infusion over 2 days). Treatment continued until disease progression or unacceptable toxicity.

The primary efficacy outcomes were overall survival (OS) and Overall Response Rate (ORR). Additional efficacy outcome measures included progression-free survival (PFS), , and duration of response (DoR) as assessed by blinded independent central review (BICR). OS and PFS were assessed in all randomised patients. ORR and DoR were assessed in the first 330 patients randomised (plus any additional patients randomised on the same day as the 330th randomised patient.).

A total of 220 patients were randomized to the BRAFTOVI/cetuximab arm and 221 to the control arm.

The median age of patients randomised to the encorafenib plus cetuximab or the control arm was 61 years (range 27-91), 47% were male, 80% were white and 15% were asian. Half had a baseline ECOG performance status of 0, 66% had received one prior line of systemic therapy and 34% had received two; 93% had previously received oxaliplatin and 52% had previously received irinotecan. Half of patients had at least 3 organs with tumour involvement at baseline.

The median duration of exposure was 3.2 months in the encorafenib plus cetuximab arm, and 1.4 months in the control arm. In the encorafenib plus cetuximab arm, the median relative dose intensity (RDI) was 98% for encorafenib and 94% for cetuximab. In the control arm, the median RDI was 85% for cetuximab, 76% for irinotecan and (in the subset of patients who received them) 75% for Folinic acid and 74% for 5-FU.

Encorafenib 300 mg in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR and PFS compared to the control arm. Efficacy results are summarised in Table 10 and Figure 3.

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

Table 12: Efficacy results from the BEACON CRC study (ARRAY-818-302)

	Encorafenib plus cetuximab	Control (irinotecan or FOLFIRI plus cetuximab)
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] p-value[b,c]	0.60 (0.41-0.88) 0.0002	
Median duration of follow-up, months (95% CI)	7.6 (6.4, 9.2)	7.2 (6.1, 8.1)
ORR (per BIRC)		
Number of patients[e]	113	107
ORR n (%) (95% CI)[f]	23 (20) (13, 29)	2 (2) (0, 7)
P-value[b,d,g]	<0.0001	
CR, n (%)	6 (5)	0
PR, n (%)	17 (15)	2 (2)
PFS (per BIRC)		
Number of patients[a]	220	221
Number of events (%)	133 (60)	128 (58)
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		
Overall Survival		
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	

	Encorafenib plus cetuximab	Control (irinotecan or FOLFIRI plus cetuximab)
CR, n (%)	7 (3.2)	0
PR, n (%)	36 (16.4)	4 (1.8)
SD, n (%)	117 (53.2)	59 (26.7)
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 = objective response rate; OS = overall survival; PR = partial response; SD = Stable disease,; BIRC = blinded independent central review

[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

Figure 3: Kaplan-Meier plot of OS in BEACON CRC (cut-off date: 11 February 2019)

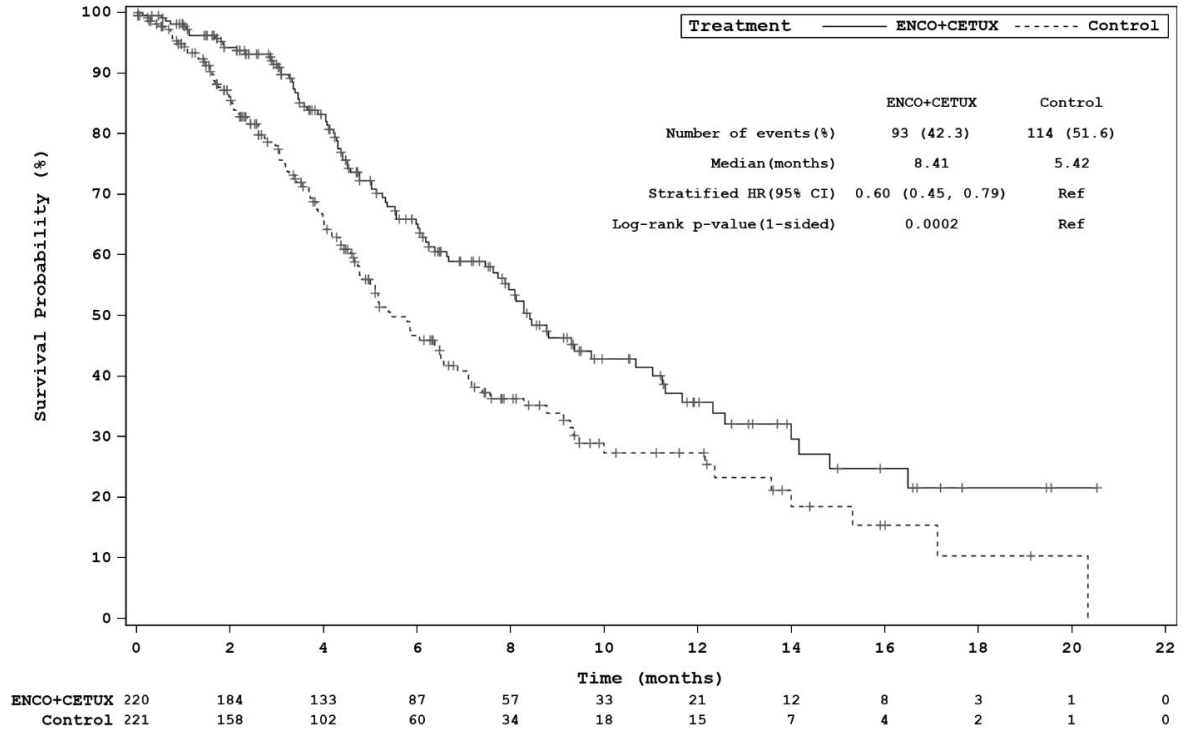
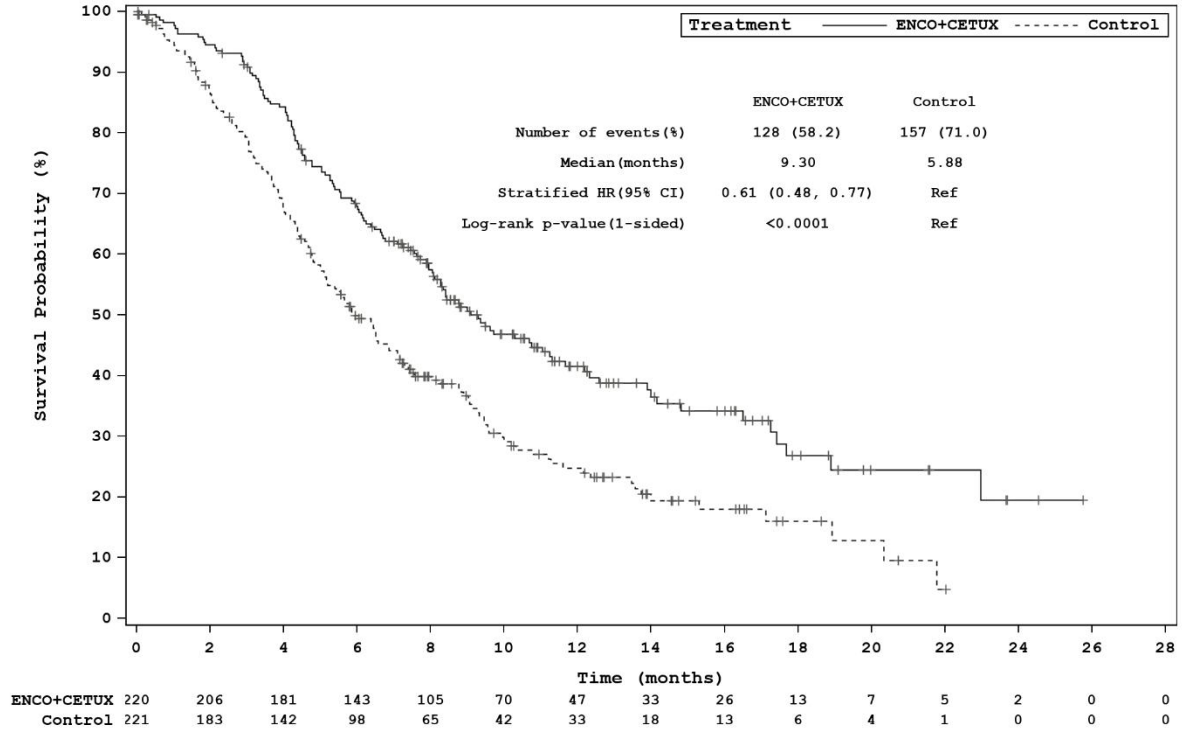


Figure 4: Study ARRAY-818-302: Kaplan-Meier plot of Overall Survival (cut-off date: 15 August 2019)



Cardiac electrophysiology

In the encorafenib plus cetuximab arm of BEACON CRC, 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 (see section 4.2 *Dose and method of administration* and section 4.4 *Special warnings and special precautions for use*).

PHAROS - BRAF V600E Mutant advanced Non-small cell lung cancer (NSCLC)

The safety and efficacy of encorafenib in combination with binimetinib were studied in a Phase II, open-label, multicentre, non-comparative study (Study ARRAY-818-202, PHAROS). Patients were required to have histologically-confirmed metastatic NSCLC with a BRAF V600E mutation, ECOG performance status of 0 or 1, and measurable disease. Patients had received 0 or 1 prior line of systemic therapy in the metastatic setting. Prior use of BRAF inhibitors or MEK inhibitors was prohibited.
Patients were enrolled based on the determination of a BRAF V600E mutation in tumour tissue or blood (e.g., ctDNA genetic testing) by a local laboratory assay. Central confirmation of the BRAF V600E mutation status (i.e. any short variant with protein effect V600E) was performed on archival or fresh tumour tissue collected at enrolment and utilized the FoundationOne CDx – F1CDx (tissue) assay.

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

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

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

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

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

Results updated with an additional 10-month follow-up (median duration of exposure of 16.3 months in treatment naïve patients and 5.5 months in previously treated patients) are provided in Table 13.

Table 13: PHAROS: Efficacy Results

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

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

Cardiac electrophysiology

The incidence of new QTcF prolongation >500 ms was 2.1% (2/95), and QTcF prolongation of >60 ms (compared to pre-treatment values) was observed in 7.3% (7/96) of patients (see section 4.2 *Dose and method of administration* and section 4.4 *Special warnings and special precautions for use*).

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of encorafenib were studied in adult healthy subjects and patients with solid tumours, including BRAF-V600E or BRAF-V600K mutant advanced and unresectable or metastatic cutaneous melanoma, BRAF V600E mutant metastatic colorectal cancer and BRAF V600E mutant metastatic non-small cell lung cancer. 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 intersubject variability (CV %) of AUC 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 maximum encorafenib concentration (C_{max}) by 36%, while the area under the concentration-time curve (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%).

Metabolism
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.

Excretion
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).

Special populations

Hepatic impairment

Results from a dedicated clinical trial indicate a 25% higher encorafenib exposure 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 section 4.2 *Dose and method of administration* and section 4.4 *Special warnings and special precautions for use*).

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 PK 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.

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.

The elderly

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

Children and adolescents (< 18 years)

The pharmacokinetics of encorafenib have not been established in patients below the age of 18 years.

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.

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.

Race
There have been no clinically relevant differences in encorafenib PK observed specifically in the Asian population. There are insufficient data to evaluate potential differences in the exposure of encorafenib on the basis of race or ethnicity.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity
Based on the results of *in vitro* bacterial reverse mutation assays, an *in vitro* human peripheral blood lymphocyte chromosomal aberration assay and an *in vivo* rat bone marrow micronucleus test, encorafenib is not genotoxic.

Carcinogenicity
The carcinogenic potential of encorafenib was not evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

BRAFTOVI capsules are capsules for oral administration. Each capsule contains 50 or 75 mg encorafenib. The capsules also contain the excipients: copovidone, poloxamer, microcrystalline cellulose, succinic acid, crospovidone, colloidal anhydrous silica and magnesium stearate; the capsule shell contains the excipients: gelatin, titanium dioxide, iron oxide red, iron oxide yellow and iron oxide black; and the printing ink contains the excipients: shellac, iron oxide black, propylene glycol.

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

Store in original container.

6.5. NATURE AND CONTENTS OF CONTAINER

Braftovi 50 mg capsules
Polyamide/aluminium/PVC/ aluminium/PET/paper perforated unit dose blisters containing 4 capsules.
Each pack contains 28 capsules

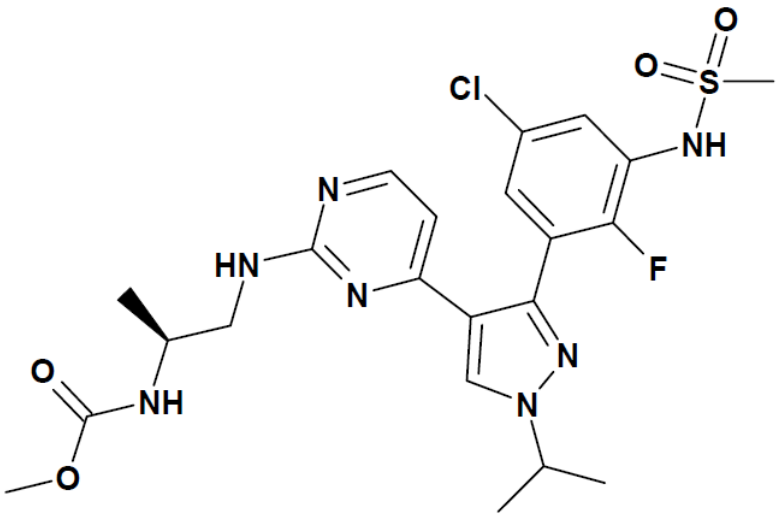
Braftovi 75 mg capsules
Polyamide/aluminium/PVC/ aluminium/PET/paper perforated unit dose blister containing 6 capsules.
Each pack contains 42 capsules

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Abstracts Service (CAS) registry number
1269440-17-6

Chemical name
Methyl *N*-[(1*S*)-2-[[4-[3-[5-chloro-2-fluoro-3-[(methylsulfonyl)amino]phenyl]-1-(1-methylethyl)-1*H*-pyrazol-4-yl]-2-pyrimidinyl]amino]-1-methylethyl]carbamate

Encorafenib is a white to almost white powder with the molecular formula $C_{22}H_{27}ClFN_7O_4S$ and a molecular weight of 540.0. It is slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2 (0.01 to 0.1%), and insoluble at pH 3 and above. Its dissociation constants (pKa) are 4.49 and 7.21. Encorafenib is not hygroscopic.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8. SPONSOR

Pierre Fabre Australia Pty Limited
Level 7, 32 Walker St
North Sydney NSW 2060
Australia

9. DATE OF FIRST APPROVAL

3 January 2019

10. DATE OF REVISION

28 November 2025

Summary table of changes

Section changed	Summary of new information
4.2	Change of Posology of second dose reduction to 225 mg for melanoma indication
4.8	Update on Elderly patients part based on EU renewal
4.1, 4.2, 4.8, 5.1 and 5.2	Updated based on the addition of therapeutic indication for treatment of metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation and dosage change.