▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

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

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

4.2. DOSE AND METHOD OF ADMINISTRATION

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

Dosage
Patients treated with encorafenib must have their BRAF V600 mutant melanoma status confirmed by a validated test, conducted by an experienced laboratory (see 5.1 Clinical trials).
The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily when used in combination with binimetinib.

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 (see Tables 1 and 2).

Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, reduce encorafenib to 300 mg once daily during the time of binimetinib dose interruption (see section 4.2 *Dose and method of administration* of binimetinib PI) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib may be continued (at the reduced dose of 300 mg) depending on the individual clinical benefit.

If encorafenib is temporarily interrupted, interrupt binimetinib. If encorafenib is permanently discontinued, then discontinue binimetinib.

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

Dose reduction recommendations for encorafenib are presented in Table 1.

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

Dose level	**Encorafenib dose** when used in combination with binimetinib
Starting dose	450 mg once daily
1st dose reduction	300 mg once daily
2nd dose reduction	200 mg once daily
Subsequent modification	Permanently discontinue encorafenib and binimetinib if unable to tolerate 200 mg once daily
Dose re-escalation	• If the encorafenib dose has been reduced to 300 mg once daily, it may be re-escalated to 450 mg once daily if: – the adverse reaction that resulted in dose reduction has recovered to baseline level; – there are no other concomitant encorafenib-related toxicities that would prevent drug re-escalation and; – binimetinib is continued. • If the encorafenib dose has been reduced to 200 mg once daily, it may be re-escalated to 300 mg once daily if: – the adverse reaction that resulted in dose reduction has recovered to baseline level and; – there are no other concomitant encorafenib-related toxicities that would prevent drug re-escalation. • The encorafenib dose should not be re-escalated if the dose reduction is due to QTcF prolongation or any Grade 4 toxicity.

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

For new primary cutaneous malignancies: No dose modification is required

For new primary non-cutaneous RAS mutation-positive malignancies: Consider permanently discontinuing encorafenib and binimetinib.

If treatment-related toxicities occur when encorafenib is used in combination with binimetinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modification is necessary for binimetinib only (adverse reactions primarily related to binimetinib) are: retinal pigment epithelial detachment (RPED),

retinal vein occlusion (RVO); interstitial lung disease/pneumonitis; cardiac dysfunction; creatine phosphokinase (CK) elevation; rhabdomyolysis and venous thromboembolism.

If one of these toxicities occurs, see section 4.2 *Dose and method of administration* of binimetinib PI for dose modification instructions for binimetinib.

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

Severity of adverse reaction[a]	**Recommended encorafenib dose modification**
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.
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 and

	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	
QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Withhold encorafenib, see monitoring in section 4.4 *Special warnings and special precautions for use.* Resume encorafenib at a reduced dose when QTcF ≤ 500 ms. Encorafenib should be discontinued if more than one recurrence.
QTcF> 500 ms and increased by > 60 ms from pre-treatment values	Permanently discontinue encorafenib (see monitoring in section 4.4 *Special warnings and special precautions for use)*
Liver laboratory abnormalities	
Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x – ≤ 5 x upper limit of normal (ULN))	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.
First occurrence of Grade 3 (AST or ALT >5x ULN and blood bilirubin >2x ULN)	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, it should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
First occurrence of Grade 4 (AST or ALT >20 ULN)	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued.

	Or, encorafenib should be permanently discontinued.
Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue encorafenib.
Recurrent Grade 4 (AST or ALT > 20 ULN)	Encorafenib should be permanently discontinued
Other	
• 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, resume at a reduced dose. • If not improved, permanently discontinue encorafenib.
• First occurrence of any Grade 4 adverse reaction	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.

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 reduced dose of 300 mg once daily in patients with mild hepatic impairment (Child-Pugh Class A).

No dosing recommendation can be made in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment based on a population pharmacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential 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

When encorafenib is given in combination with binimetinib, the PI for binimetinib must be consulted prior to initiation of combination treatment. For additional information on warnings and precautions associated with binimetinib treatment, please refer to the PI for binimetinib.

BRAF mutation testing
Before taking encorafenib, patients must have their BRAF V600 mutant melanoma status confirmed by a validated test to minimise false-positive and false-negative determinations. The efficacy and safety of encorafenib were only established in patients with tumours expressing BRAF V600E and V600K mutations. Encorafenib should not be used in patients with wild-type BRAF malignant melanoma.

Encorafenib in combination with binimetinib in patients who have progressed on a BRAF inhibitor
There are limited data 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.

Encorafenib in combination with binimetinib in patients with 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 with brain metastases (see section 5.1 *Pharmacodynamic properties*).

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.

It is recommended that LVEF (left ventricular ejection fraction) is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of encorafenib and binimetinib, one month after initiation and then at approximately 3-month intervals or more frequently as clinically indicated while on treatment. If LVD occurs during treatment, see section 4.2 *Dose and method of administration* of PI for binimetinib.

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 (LLN). Therefore, in these patients, binimetinib should be used with caution and for any symptomatic LVD, Grade 3 or 4 LVEF or for absolute decrease of LVEF from baseline of ≥ 10%, binimetinib, and encorafenib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Haemorrhage
Haemorrhages, including major haemorrhagic events, can occur when encorafenib is administered in combination with binimetinib (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. RPED was also reported in patients treated with encorafenib in combination with binimetinib (see section 4.8 *Adverse effects (undesirable effects)*). Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended.

If uveitis including iridocyclitis and iritis occurs during treatment, see section 4.2 *Dose and method of administration* for guidance.

If RPED or RVO develop during treatment, see section 4.2 *Dose and method of administration* of the binimetinib PI for guidance.

QT prolongation
QT prolongation has been observed in patients treated with BRAF-inhibitors. A thorough QT study to evaluate the QT prolongation potential of encorafenib has not been conducted. Overall, results suggest that single agent encorafenib has the potential to cause mild increases in heart rate. Across pooled combination studies of encorafenib and binimetinib at the recommended doses and a single-agent encorafenib study, results suggest that encorafenib has the potential to result in small increases in QTc interval (see section 5.1 *Pharmacodynamic properties*).
There are insufficient data to exclude a clinically significant exposure dependent QT prolongation.
Due to the potential risk for QT prolongation, it is recommended that serum electrolytes abnormalities, including magnesium and potassium, are corrected and risk factors for QT prolongation controlled (e.g. congestive heart failure, bradyarrhythmias) before treatment initiation and during treatment.

It is recommended that an electrocardiogram (ECG) is assessed before initiation of encorafenib, one month after initiation, and then at approximately 3-month intervals or more frequently, as clinically indicated, while on treatment. The occurrence of QTc prolongation can be managed with dose reduction, treatment interruption or treatment discontinuation with correction of abnormal electrolytes and control of risk factors (see section 4.2 *Dose and method of administration*).

New primary malignancies
New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when encorafenib is administered as a single agent or when used in combination with binimetinib.

Cutaneous malignancies
Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including kerathoacanthoma have been observed in patients treated with BRAF-inhibitors including encorafenib. New primary melanoma has been observed in patients treated with BRAF-inhibitors including encorafenib (see section 4.8 *Adverse effects (undesirable effects)*).

Dermatologic evaluations should be performed prior to initiation of therapy with encorafenib in combination with binimetinib every 2 months while on therapy and for up to 6 months following discontinuation of the combination. Suspicious skin lesions should be managed by dermatological excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Encorafenib and binimetinib should be continued without any dose modification.

Non-cutaneous malignancies
Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving encorafenib

should undergo a head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate. 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.

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 reduced dose in patients with mild hepatic impairment (see section 4.2 *Dosage 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. 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 2 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 yet 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 binimetinib 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

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).

CYP3A4 inhibitors
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 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. Examples of moderate or strong CYP3A4 inducers include, but are not limited to carbamazepine, rifampicin, phenytoin and St. John's Wort. Alternative agents with no or minimal CYP3A induction should be considered.

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 substrates

Encorafenib is both an inhibitor and inducer of CYP3A4. *In vitro* experiments indicate 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. Simulations of 450 mg encorafenib co-administered with probe substrates for CYP2B6, CYP1A2, CYP2C9,CYP2C19 and CYP2D6 on Day 1 and Day 15 all indicated no clinically relevant interactions are expected. For co-administration with CYP3A4 and UGT1A1 substrates that undergo gut extraction, a minor to moderate interaction is expected.

Concomitant use with agents that are substrates of CYP3A4 (e.g. hormonal contraceptives) may result in increased toxicity or loss of efficacy of these agents.
Agents that are CYP3A4 substrates should be co-administered with caution.

As encorafenib is an inhibitor of UGT1A1, agents that are substrates of UGT1A1 should be administered with caution.

Effect of encorafenib on binimetinib

When binimetinib was co-administered with encorafenib, no difference in binimetinib exposure was observed. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction and therefore no interaction with encorafenib is expected.

Transporter substrates

Encorafenib potentially inhibits a number of transporters. Based on *in vitro* studies, there is potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 and hepatic transporters OCT1, OATP1B1 and OATP1B3 at clinical concentrations. In addition, encorafenib may inhibit breast cancer resistance protein (BCRP) at the expected clinical concentrations.

Agents that are transporter substrates (OCT2, OAT1, OAT3, OATP1B1, OATP1B3 and BCRP) should be co-administered with caution.

Encorafenib is a weak inhibitor of P-gp, but at high concentrations in the intestine, it may increase oral absorption of drugs that are P-gp substrates.

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 breast feeding 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
The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 274 patients with BRAF V600 mutant unresectable or metastatic melanoma (hereafter referred to as the pooled Combo 450 population), based on two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301).

At the recommended Combo 450 dose in patients with metastatic melanoma (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 myalgia.

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

The encorafenib single agent (300 mg once daily) safety profile is based on data from 3 clinical studies 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 were

hyperkeratosis, alopecia, PPES fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus.

Tabulated summary of adverse reactions

Adverse reactions in the pooled Combo 450 population (n=274) and in the pooled encorafenib 300 mg population (n=217) are listed in Table 3, by MedDRA body system organ class (SOC).

Table 3: Adverse reactions occurring in patients receiving encorafenib alone (n = 217) or encorafenib in combination with binimetinib at the recommended doses (n = 274)

Frequency	**Encorafenib single agent 300 mg (n=217)**		**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 nevus	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
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)

Frequency	Encorafenib single agent 300 mg (n=217)		Encorafenib 450 mg in combination with binimetinib (n=274)	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
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)		
Muscular disorders/Myalgia[l]			71 (25.9)	2 (0.7)
Pain in extremity	46 (21.2)	2 (0.9)	29 (10.6)	4 (1.5)
Back pain	33 (15.2)	5 (2.3)	30 (10.9)	2 (0.7)
Arthritis *	11 (5.1)	3 (1.4)	4 (1.5)	0
Rhabdomyolysis	0	0	1 (0.4)	1 (0.4)
Renal and urinary disorders				
Renal failure *	6 (2.8)	3 (1.4)	9 (3.3)	6 (2.2)
General disorders and administration site conditions				
Fatigue*	95 (43.8)	10 (4.6)	120 (43.8)	8 (2.9)
Pyrexia*	33 (15.2)	2 (0.9)	47 (17.2)	8 (2.9)
Peripheral oedema[m]	22 (10.1)	0	42 (15.3)	3 (1.1)

Frequency	Encorafenib single agent 300 mg (n=217)		Encorafenib 450 mg in combination with binimetinib (n=274)	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
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
[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

Description of selected adverse reactions

Cutaneous malignancies

Cutaneous squamous cell carcinoma

In the pooled Combo 450 population, cuSCC including keratoacanthomas was observed in 3.3% (9/274) of patients. The median time to onset of the first event of cuSCC (all grades) was 6.5 months (range 1 to 22.8 months).

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

New primary melanoma

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

Ocular events

In the pooled Combo 450 population, RPED was reported in 29.6 % (81/274) of patients. RPED was Grade 1 (asymptomatic) in 21.2% (58/274) of patients, Grade 2 in 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.

Left ventricular dysfunction

LVD was reported when encorafenib is used in combination with binimetinib (see section 4.8 *Adverse effects (undesirable effects)* of binimetinib PI).

Haemorrhage

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 study CMEK162B2301-Part 2, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3 or 4 in 1.6% (4/257) of patients.

Hypertension

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

Venous thromboembolism

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

Pancreatitis

Pancreatic enzyme elevation, mostly asymptomatic, was reported in the pooled Combo 450 population. Amylase and lipase elevations have been reported in 3.3% (9/274) and 51% (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 or adjustment in 0.4% (1/274) of patients.

Dermatological reactions

Rash

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 mg 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.

Palmar-plantar erythrodysaesthesia syndrome

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 mg 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.

Dermatitis acneiform

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

Photosensitivity

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.

Facial paresis

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

In the pooled encorafenib 300 population, facial paresis was observed in 7.4% (16/217) of patients. Most events were mild 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.

CK elevation /Rhabdomyolysis

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

Renal dysfunction

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 with Grade 3 or 4 events in 2.2% (6/274) of patients. Renal failure was generally reversible with dose interruption, rehydration and other general supportive measures.

Liver laboratory abnormalities

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

- Increased ALT: 13.1 % (36/274) overall - Grade 3-4: 4.7 % (13/274)
- Increased AST: 9.5 % (26/274) overall - Grade 3-4: 2.2 % (6/274)
- Increased GGT: 14.6 % (40/274) overall - Grade 3-4: 8.4 % (23/274)
- Increased bilirubin: 0.7 %(2/274) overall - the maximum severity of these events was Grade 2

Gastrointestinal disorders

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

Gastrointestinal disorders were typically managed with standard therapy.

Anaemia

In the pooled Combo 450 population, anaemia was reported in 19.7% (54/274) of patients; 4.7% (13/274) patients had a Grade 3 or 4. No patients discontinued treatment due to anaemia, 1.5% (4/274) required dose interruption or dose modification. In the Combo 300 population of study CMEK162B2301, Part 2, anaemia was observed in 9.7% (25/257) of patients with Grade 3 or 4 reported in 2.7% (7/257) of patients.

Headache

In the pooled Combo 450 population, headache occurred in 21.5% (59/274) of patients, including Grade 3 in 1.5% (4/274) of patients. In the Combo 300 population of study

CMEK162B2301, Part 2 headache was reported in 12.1% (31/257) of patients and was Grade 3 in 0.4% (1/257) of patients.

Fatigue
In the pooled Combo 450 population, fatigue occurred in 43.8% (120/274) of patients including Grade 3 in 2.9% (8/274) of patients. In the Combo 300 population of study CMEK162B2301, Part 2, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3 or 4 events.

Adverse events

Table 4 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 in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma (CMEK162B2301).

Table 4: Treatment-emergent adverse events occurring very commonly (≥10% any grade or ≥2 % grades 3 or 4) of patients receiving Combo 450 mg, Enco 300 mg or vemurafenib in Part 1 of study CMEK162B2301

	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)
GT 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)

	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
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)
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.

In Part 1 of study CMEK162B2301, serious adverse events (SAEs) regardless of relationship to study therapy were reported in 35.9% of patients 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.

Special populations

The elderly

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. The proportions of patients experiencing AEs and SAEs were similar in patients aged <65 years and those aged ≥65 years. The most common AEs reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included diarrhoea, pruritus, GGT and blood phosphatase alkaline elevation. In the small group of patients aged ≥75 years (n=15), patients were more likely to experience SAEs and AEs leading to discontinuation of treatment.

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 hypercreatinemia) 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: not yet assigned

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. *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.

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. Additionally, the combination of encorafenib and binimetinib prevented the emergence of treatment resistance in BRAF V600E mutant human melanoma xenografts in mice.

Cardiac electrophysiology

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

Clinical trials

BRAF V600 mutant unresectable or metastatic melanoma

The safety and efficacy of encorafenib in combination with binimetinib were evaluated in 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 (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.

Patients in the study 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). 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.

Study CMEK162B2301 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 5 and Figure 1 summarise the PFS and other efficacy results based on central review of the data by the BIRC.

Table 5: Progression-free survival and confirmed overall response results, cut-off date: 19 May 2016 (independent central review)

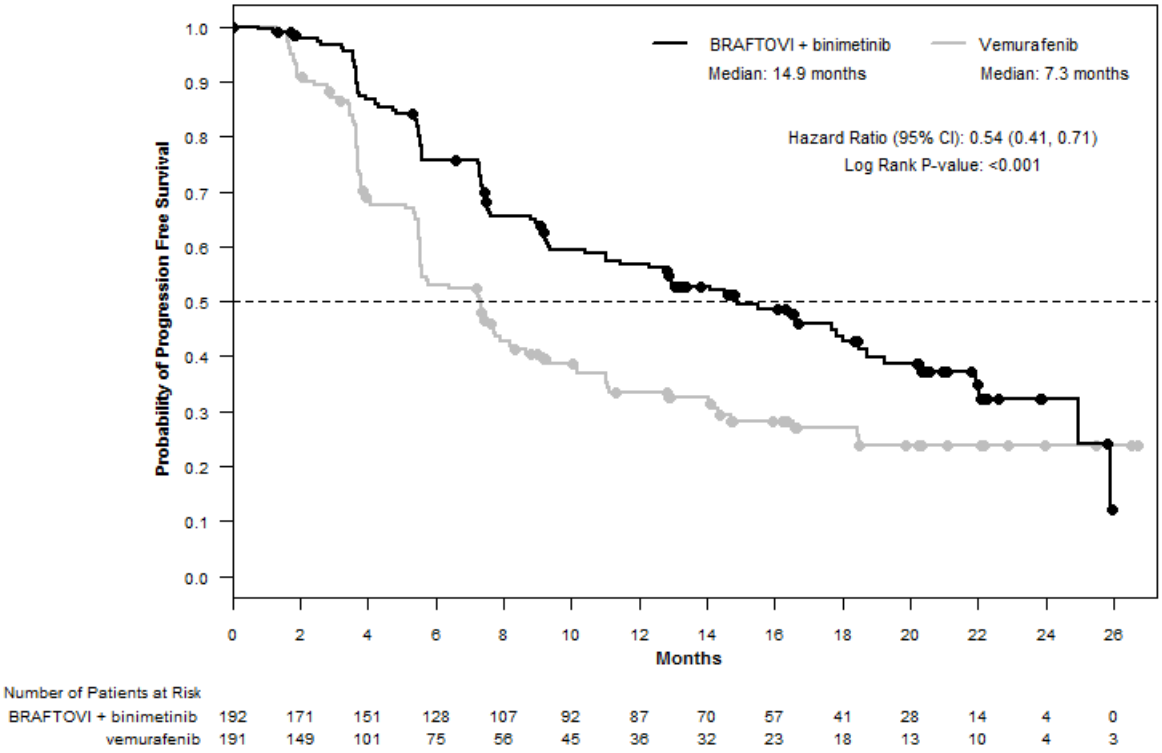
	Combo 450 Encorafenib and binimetinib N = 192	**Enco 300 Encorafenib N = 194**	**Vem N = 191**
Progression free survival			
Number of events (progressive disease (PD)) (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	7.3 (5.6, 8.2)
HR[a] (95% CI) (vs. Vem) P value (stratified log-rank)[b]	0.54 (0.41, 0.71) <0.001		
HR[a] (95 % CI) (vs. Vem) Nominal p-value		0.68 (0.52, 0.90) 0.007	
HR[a] (95% CI) (vs. Enco 300) P value (stratified log-rank)[b]	0.75 (0.56,1.00) 0.051		
Confirmed Overall Responses			
Overall Response Rate, n (%) (95% CI)	121 (63.0) (55.8, 69.9)	98 (50.5) (43.3, 57.8)	77 (40.3) (33.3, 47.6)
CR, n (%)	15 (7.8)	10 (5.2)	11 (5.8)
PR, n (%)	106 (55.2)	88(45.4)	66 (34.6)
SD, n (%)	46 (24.0)	53(27.3)	73 (38.2)
DCR, n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	156 (81.7) (75.4, 86.9)
Duration of Response			
Median, months (95% CI)	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)

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 results by investigator assessment are summarised in Table 6.

Table 6: Progression-free survival and confirmed overall response results, cut-off date: 19 May 2016 (investigator assessment)

	Combo 450 Encorafenib and binimetinib N = 192	**Enco 300 Encorafenib N = 194**	**Vem Vemurafenib N = 191**
Progression free survival			
Number of events (progressive disease(PD)) (%)	102 (53.1)	108(55.7)	121 (63.4)
Median, months (95% CI)	14.8 (10.4, 18.4)	9.2 (7.4,12.9)	7.3 (5.7, 8.5)
HR[a] (95% CI) (vs. Vem) *P* value (stratified log-rank)[b]	0.49 (0.37, 0.64) <0.001		

HR[a] (95% CI) (vs. Enco 300) *P* value (stratified log-rank)[b]	0.68 (0.52, 0.90) 0.006		
Confirmed Overall Responses			
Overall Response Rate, n (%) (95% CI)	144 (75.0) (68.3, 81.0)	112 (57.7) (50.4, 64.8)	94 (49.2) (41.9, 56.5)
CR, n (%)	31 (16.1)	17 (8.8)	14 (7.3)
PR, n (%)	113 (58.9)	95 (49.0)	80 (41.9)
SD, n (%)	35 (18.2)	55 (28.4)	65 (34.0)
DCR, n (%) (95% CI)	179 (93.2) (88.7, 96.3)	168 (86.6) (81.0, 91.1)	160 (83.8) (77.8, 88.7)

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)

At a cut-off date of 07 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 study CMEK162B2301 Part 1, performed at the cut-off date of 07 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 7 and Figure 2]).

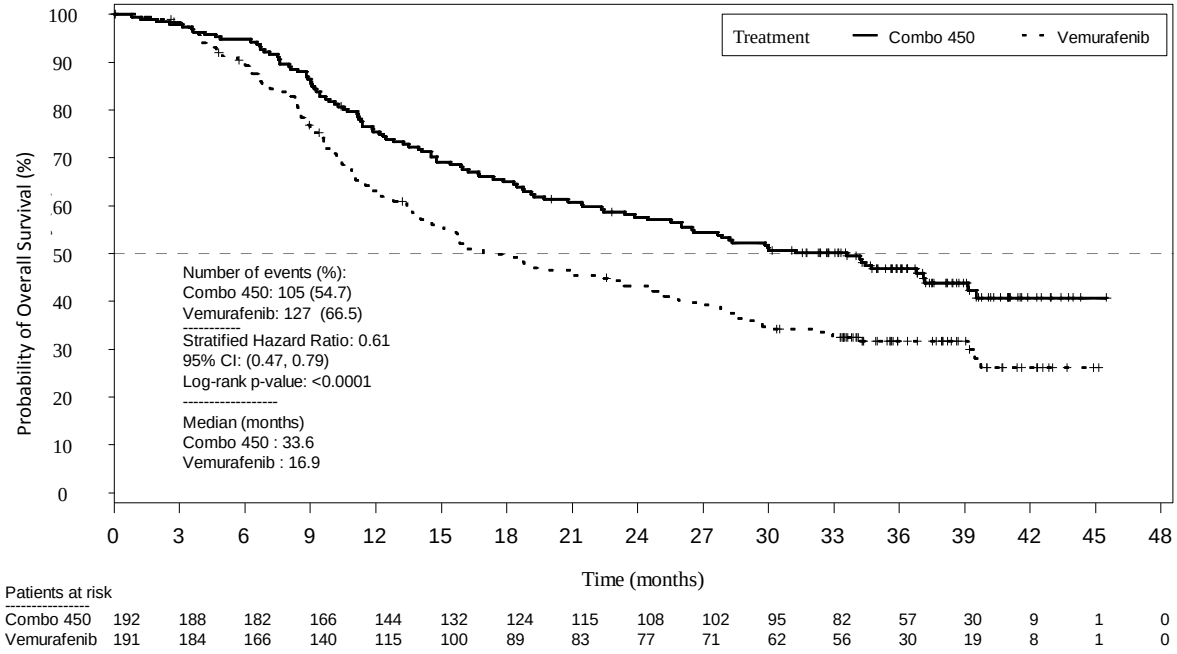
A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4% Combo 450 arm, 36.1% Enco 300 arm, 39.8% vemurafenib arm).

Table 7: 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).

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumours, including advanced and unresectable or metastatic cutaneous melanoma harbouring a BRAF-V600E or BRAF-V600K mutation. The pharmacokinetics of encorafenib have been shown to be approximatively dose linear after single and multiples doses. After repeat once-daily dosing, steady-state conditions were reached within 15 days. The accumulation ratio of approximately 0.5 is likely due to auto-induction of CYP3A4. The 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 (Cmax) 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 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 – aluminum blister containing 4 capsules.
Each pack contains 28 capsules

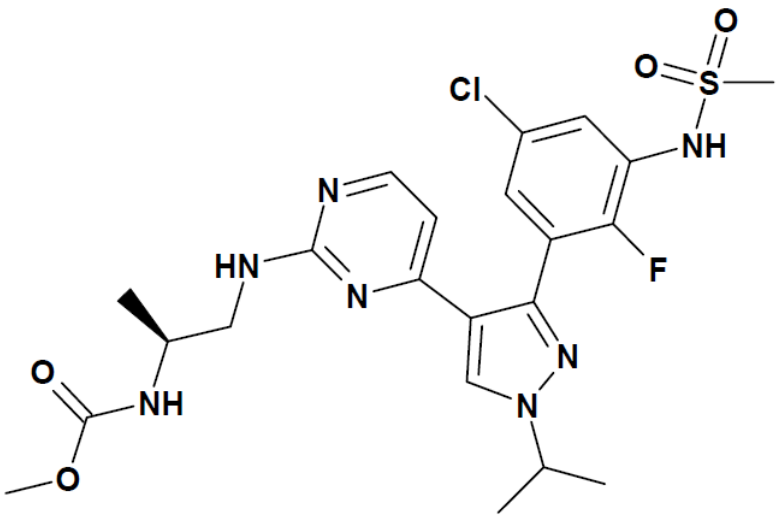
Braftovi 75 mg capsules
Polyamide/aluminium/PVC – aluminum blister containing 6 capsules.
Each pack contains 42 capsules

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 has 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
901/1 Elizabeth Plaza
North Sydney NSW 2060
Australia

9. DATE OF FIRST APPROVAL

3 January 2019

10. DATE OF REVISION

1 August 2019

Summary table of changes

Section changed	Summary of new information
6.4	Update of storage condition.