▼ 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
MEKTOVI (binimetinib) film-coated tablets

1. NAME OF THE MEDICINE

Binimetinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MEKTOVI film-coated tablet contains binimetinib 15mg.

Contains lactose. Contains sugars. For a full list of excipients, see section 6.1 *List of excipients.*

3. PHARMACEUTICAL FORM

MEKTOVI 15 mg film-coated tablets are yellow/dark yellow, unscored biconvex, ovaloid film-coated tablets, approximately 12 mm in length and 5 mm in width, with the “A” logo debossed on one face of the tablet and “15” on the opposing face.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

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

Dosage
Patients treated with binimetinib in combination 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 binimetinib is 45 mg (three 15 mg tablets) twice daily (corresponding to a total dose of 90 mg), approximately 12 hours apart, when used in combination with encorafenib.

Administration
Binimetinib tablets should be swallowed whole with water, with or without food.

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

Missed dose
If a dose of binimetinib is missed, it should not be taken if it is less than 6 hours until the next dose is due.

Vomiting after administration
If a patient vomits after administration of binimetinib, the patient should not take the dose again. 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 below and Table 1). The decision on whether to modify the dose of binimetinib should be based on the prescriber's assessment of individual patient safety and tolerance.

The recommended reduced dose of binimetinib is 30 mg twice daily. Dose reduction below 30 mg twice daily is not recommended. Therapy should be discontinued if the patient is not able to tolerate 30 mg orally twice daily.

If the adverse reaction that resulted in a dose reduction is under effective management, re-escalation to 45 mg twice daily may be considered. Dose-re-escalation to 45 mg twice daily is not recommended if the dose reduction is due to left ventricular dysfunction (LVD) or any Grade 4 toxicity.

If treatment-related toxicities occur when binimetinib is used in combination with encorafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for encorafenib only (adverse reactions primarily related to encorafenib) are: palmar-plantar erythrodysaesthesia syndrome (PPES), uveitis including iritis and iridocyclitis, and QTc prolongation.

If one of these toxicities occurs, see section 4.2. *Dose and Method of Administration* of encorafenib PI for dose modification instructions for encorafenib.

If binimetinib is temporarily interrupted, reduce encorafenib to 300 mg once daily during the time of binimetinib dose interruption (see Table 1) 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 (see section 4.2 *Dose and Method of Administration* of encorafenib PI), interrupt binimetinib. If encorafenib is permanently discontinued, then discontinue binimetinib.

Dose modification recommendations in case of adverse reactions are presented in Table 1. For information on the dosage and recommended dose modifications of encorafenib, refer to the encorafenib PI, section 4.2 *Dose and Method of Administration*.

Table 1: Recommended dose modification for adverse reactions with binimetinib (used in combination with encorafenib) for selected adverse reactions

Severity of adverse reaction[a]	**Recommended binimetinib dose modification**
Cutaneous reactions	
Grade 2	Maintain binimetinib If rash worsens or does not improve within 2 weeks with treatment, withhold binimetinib until Grade 0 or 1 and then resume at the same dose if first occurrence or resume at a reduced dose if recurrent Grade 2.
Grade 3	Withhold binimetinib 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 binimetinib.
Ocular events	
• Symptomatic retinal pigment epithelial detachment (RPED) (Grade 2 or 3)	Withhold binimetinib for up to 2 weeks and repeat ophthalmic monitoring including visual acuity assessment. • If improved to Grade 0 or 1, resume binimetinib at same dose • If improved to Grade 2, binimetinib should be resumed at a lower dose. • If not improved to Grade 2, binimetinib should be permanently discontinued.

• Symptomatic RPED (Grade 4) associated with reduced visual acuity	Permanently discontinue binimetinib.
• Retinal vein occlusion (RVO)	Permanently discontinue binimetinib.
Cardiac events	
• Grade 2 left ventricular ejection fraction (LVEF) decrease or asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is below lower limit of normal (LLN)	Evaluate LVEF every 2 weeks. • If asymptomatic: Withhold binimetinib for up to 4 weeks. : Resume binimetinib at a reduced dose if all of the following are present within 4 weeks: o LVEF at or above the LLN and o Absolute decrease from baseline is 10% or less. • If the LVEF does not recover within 4 weeks, permanently discontinue binimetinib.
• Grade 3 or 4 LVEF decrease or symptomatic LVD	Permanently discontinue binimetinib. Evaluate LVEF every 2 weeks until recovery.
Rhabdomyolysis/Creatine phosphokinase (CK) elevation	
• Grade 3 (CK > 5 – 10 x upper limit of normal (ULN) asymptomatic	Maintain binimetinib dose and ensure patient is adequately hydrated.
• Grade 4 (CK > 10 x ULN) asymptomatic	Withhold binimetinib until improved to Grade 0 or 1. Ensure patient has adequate hydration.
• Grade 3 or 4 (CK > 5 x ULN) with muscle symptoms or renal impairment	Withhold binimetinib until improved to Grade 0 or 1 • If resolved within 4 weeks, resume binimetinib at a reduced dose, or • Permanently discontinue binimetinib.
Venous thromboembolism	
• Uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) ≤ Grade 3	Withhold binimetinib • If improved to Grade 0 or 1, resume at a reduced dose. • If not improved, permanently discontinue binimetinib.
• Grade 4 PE	Permanently discontinue binimetinib.
Liver laboratory abnormalities	
• Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase	Maintain binimetinib dose If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0 or 1 or to baseline levels, and then resume at the same dose.

(ALT) > 3 x – ≤ 5 x upper limit of normal (ULN)	
• First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, resume binimetinib at reduced dose, or • If not improved, permanently discontinue binimetinib.
• First occurrence of Grade 4 (AST or ALT > 20 ULN)	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, resume binimetinib at a reduced dose level, or • If not improved, permanently discontinue binimetinib. Or, binimetinib should be permanently discontinued.
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Consider permanently discontinuing binimetinib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Permanently discontinue binimetinib.
Interstitial lung disease (ILD)/pneumonitis	
• Grade 2	Withhold binimetinib for up to 4 weeks • If improved to Grade 0 or 1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.
Grade 3 or 4	Permanently discontinue binimetinib.
Other	
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Withhold binimetinib for up to 4 weeks • If improved to Grade 0 or 1 or baseline level, resume at a reduced dose. • If not improved, permanently discontinue binimetinib.
• First occurrence of Grade 4 adverse reactions	Withhold binimetinib 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 binimetinib. Or, permanently discontinue binimetinib.
• Recurrent Grade 3 adverse reactions	Consider permanently discontinuing binimetinib.
• Recurrent Grade 4 adverse reactions	Permanently discontinue binimetinib.

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

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A). As encorafenib is not recommended in patients with moderate (Child Pugh B) or severe hepatic impairment (Child-Pugh C), administration of binimetinib is not recommended in these patients (see section 4.2 *Dose and method of administration* of encorafenib PI).

Renal impairment
No dose adjustment is required for patients with renal impairment (see 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 binimetinib 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 binimetinib or to any of the excipients (see section 6.1 *List of excipients*).

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

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

BRAF mutation testing
Before taking binimetinib in combination with 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 binimetinib in combination with encorafenib were only established in patients with tumours expressing BRAF V600E and V600K mutations. Binimetinib in combination with encorafenib should not be used in patients with wild-type BRAF malignant melanoma.

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

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

Left ventricular dysfunction
Left ventricular dysfunction, defined as symptomatic or asymptomatic decreases in ejection fraction can occur with the use of binimetinib.

It is recommended that LVEF is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of binimetinib, 1 month after initiation and then at approximately 3-month intervals or more frequently as clinically indicated while on treatment. The occurrence of LVEF decrease can be managed with dose reduction, treatment interruption or treatment discontinuation (see section 4.2 *Dose and method of administration*).

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

Venous thromboembolism
Venous thromboembolism (VTE) can occur with the use of binimetinib. (see section 4.8 *Adverse effects (undesirable effects*)). Binimetinib should be used with caution in patients who are at risk of, or with a history of VTE.

If during treatment the patient develops VTE or pulmonary embolism, it should be managed with dose reduction, treatment interruption or treatment discontinuation (see section 4.2 *Dose and method of administration*).

Haemorrhage
Haemorrhages, including major haemorrhagic events, can occur when binimetinib is administered 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 should be managed with dose

reduction, treatment or treatment discontinuation; as clinically indicated (see section 4.2 *Dose and method of administration*).

Ocular toxicities
Ocular toxicities including RPED and RVO can occur when binimetinib is administered. Uveitis, including iridocyclitis and iritis, was reported in patients treated with binimetinib in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)*).

Binimetinib is not recommended in patients with a history of RVO**.** The safety of binimetinib has not been established in patients with predisposing factors for RVO including uncontrolled glaucoma, ocular hypertension, uncontrolled diabetes mellitus or a history of hyperviscosity or hypercoagulability syndromes. Binimetinib should therefore be used with caution in these patients.

Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended.

The occurrence of symptomatic RPED can be managed with dose reduction, treatment interruption or treatment discontinuation (see Table 1 in section 4.2 *Dose and method of administration*).
Binimetinib should be permanently discontinued with the occurrence of RVO (see Table 1 in section 4.2 *Dose and method of administration*).

If a patient develops uveitis during treatment, see section 4.2 of encorafenib PI for guidance.

CK elevation and rhabdomyolysis
Asymptomatic CK elevations are seen in patients treated with binimetinib in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects*)). Across clinical trials of binimetinib in combination with encorafenib, rhabdomyolysis was uncommonly reported. Special attention should be paid to the use of binimetinib in patients with neuromuscular conditions associated with CK elevation and rhabdomyolysis.

CK and creatinine levels should be monitored monthly during the first 6 months of treatment and as clinically indicated. The patient should be advised to maintain an adequate fluid intake during treatment. Depending on the severity of symptoms, degree of CK elevation or creatinine elevation, dose reduction, dose interruption or permanent discontinuation of binimetinib may be required (see 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 binimetinib is administered in combination with encorafenib.

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

Non-cutaneous malignancies
Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving binimetinib in combination with encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment as clinically appropriate. Permanent discontinuation of binimetinib and encorafenib should be considered in patients who develop RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering binimetinib in combination with encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Hypertension
Hypertension, or worsening of pre-existing hypertension, can occur with the use of binimetinib. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate. In case of severe hypertension, temporary interruption of binimetinib is recommended until hypertension is controlled (see Table 1 in section 4.2 *Dose and method of administration*).

Pneumonitis/Interstitial lung disease (ILD)
Pneumonitis/interstitial lung disease (ILD) can occur with binimetinib. Treatment with binimetinib should be withheld in patients with suspected pneumonitis or ILD, including patients presenting new or progressive pulmonary symptoms or findings such as cough, dyspnoea, hypoxia, reticular opacities or pulmonary infiltrates (see Table 1 in section 4.2 *Dose and method of administration*). Binimetinib should be permanently discontinued in patients diagnosed with treatment related pneumonitis or ILD.

Use in hepatic impairment
Liver metabolism mainly via glucuronidation is the primary route of elimination of binimetinib (see section 5.2 *Pharmacokinetic properties*). As encorafenib is not recommended in patients with moderate (Child Pugh B) and severe hepatic impairment (Child Pugh C), administration of binimetinib is not recommended in these patients (see sections 4.2 *Dose and method of administration* and 5.2 *Pharmacokinetic properties*).

Lactose intolerance
MEKTOVI contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MEKTOVI.

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 binimetinib in children and adolescents aged < 18 years have not yet been established. There are no data available.

Effects on laboratory tests
Liver laboratory abnormalities (AST, ALT elevations) can occur with binimetinib (see section 4.8 *Adverse effects (undesirable effects*)). Liver laboratory values should be monitored before initiation of binimetinib and 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*).

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of UGT1A1 and UGT2B7 inducers or inhibitors on binimetinib
Binimetinib is primarily metabolised by UGT1A1 and UGT2B7 mediated glucuronidation and to a lesser extent by CYP1A2-and CYP2C19-mediated oxidation. In a clinical study sub-analysis however, there was no apparent relationship observed between binimetinib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGT1A1 inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib C_{max} in the presence or absence of atazanavir. Since binimetinib is metabolised by multiple enzymes, the possible extent of drug interactions mediated by UGT1A1, UGT2B7, CYP1A2 or CYP2C19 is minimal and unlikely to be clinically relevant; however, as this has not been evaluated in a formal clinical study, UGT1A1 or UGT2B7 inducers (such as rifampicin and phenobarbital), UGT1A1 inhibitors (such as indinavir, atazanavir and sorafenib) and UGT2B7 inhibitors (quinidine, mefenamic acid and diclofenac) should be co-administered with caution.

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

Effect of transporters on binimetinib
In vitro experiments indicate that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein. Co-administration of binimetinib with inhibitors of these transporters may increase the plasma binimetinib concentration in patients.

No clinically relevant drug interactions have been demonstrated with binimetinib.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effect of binimetinib on fertility in humans.

Fertility studies were not conducted with binimetinib. In repeat-dose toxicity studies, no concern on reproductive organs were observed in rats or monkeys (animal: human exposure ratios up to 19 and 0.4, respectively). It is uncertain whether binimetinib may affect fertility in patients.

Women of childbearing potential
Women of childbearing potential should be advised to use effective contraception during treatment with binimetinib and for at least 1 month after the last dose. Women of childbearing potential receiving binimetinib in combination with encorafenib should be advised that encorafenib may decrease efficacy of hormonal contraceptives. 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 binimetinib in pregnant women. However, studies in animals have demonstrated reproductive toxicity. The potential embryo-foetal effects of binimetinib were evaluated in rats and rabbits. In rats, lower gestational body weight gain and foetal body weight were noted at ≥ 30 mg/kg/d and a decreased number of ossified foetal sternebrae was noted at ≥ 10 mg/kg/d (8 times the clinical exposure). The NOAEL in rats was 10 mg/kg/d. In rabbits, mortality, maternal physical signs of toxicity, lower gestational body weight and abortion were noted at ≥ 10 mg/kg/d (1.4 times the clinical exposure). From 10 mg/kg/d, the number of viable foetuses and foetal body weights were reduced and post-implantation loss and resorptions were increased. At 20 mg/kg/d, increased litter incidences of foetal ventricular septal defects, dilated aortic arch and pulmonary trunk alterations were noted. The NOAEL in rabbit was 2 mg/kg/d (0.5 times the clinical exposure).

If administered to pregnant women, binimetinib may harm the foetus. Binimetinib should not be administered during pregnancy unless the benefits for the mother clearly outweigh the risks for the foetus.

Use in lactation
It is not known if binimetinib or its active metabolite is 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 binimetinib or to discontinue nursing, 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 patients treated with binimetinib during clinical trials. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse effects that may affect their ability to drive or use machines (see section 4.8 *Adverse effects (undesirable effects*)).

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

The safety of binimetinib (45 mg orally twice daily) in combination with encorafenib (450mg orally once daily) (hereafter referred to as the pooled Combo 450 population) was evaluated in 274 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, 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 ($\geq$ 25%) occurring in patients treated with binimetinib in combination with encorafenib were fatigue, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, arthralgia, blood CK increased and myalgia.

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

Tabulated summary of adverse reactions
Adverse reactions in the pooled Combo 450 population (n=274) are listed in Table 2 by MedDRA body system organ class (SOC).

Table 2: Adverse reactions occurring in patients receiving binimetinib in combination with encorafenib at the recommended dose (n = 274)

System Organ Class	Adverse reaction	Frequency All grades n (%)	Frequency Grades 3/4 n (%)
Neoplasms benign, malignant and unspecified	CuSCC[a]	9 (3.3)	1 (0.4)
	Basal cell carcinoma[*]	3 (1.1)	0
	Skin papilloma[*]	22 (8.03)	0
Blood and lymphatic system disorders	Anaemia	54 (19.7)	13 (4.7)
Immune system disorders	Hypersensitivity[b]	9 (3.3)	0
Nervous system disorders	Neuropathy peripheral[*]	36 (13.1)	3 (1.1)
	Dizziness[*]	42 (15.3)	7 (2.6)
	Headache[*]	59 (21.5)	4 (1.5)
	Dysgeusia	18 (6.6)	0
	Facial paresis[c]	2 (0.7)	1 (0.4)
Eye disorders	Visual impairment[*]	59 (21.5)	1 (0.4)
	RPED[*]	81 (29.6)	5 (1.8)
	Uveitis[*]	12 (4.4)	1 (0.4)
Cardiac disorders	Left ventricular dysfunction[d]	23 (8.4)	3 (1.1)
Vascular disorders	Haemorrhage[e]	49 (17.9)	9 (3.3)
	Hypertension[*]	32 (11.7)	15 (5.5)
	Venous thromboembolism[f]	13 (4.7)	3 (1.1)
Gastrointestinal disorders	Abdominal pain[*]	75 (27.4)	7 (2.6)
	Diarrhoea[*]	104 (38.0)	9 (3.3)
	Vomiting[*]	77 (28.1)	6 (2.2)
	Nausea	114 (41.6)	7 (2.6)
	Constipation	66 (24.1)	0
	Colitis[g]	6 (2.2)	2 (0.7)
	Pancreatitis[*]	2 (0.7)	2 (0.7)
Skin and subcutaneous tissue disorders	Hyperkeratosis [*]	57 (20.8)	1 (0.4)
	Rash [*]	54 (19.7)	2 (0.7)
	Dry skin[*]	40 (14.6)	0
	Pruritus[*]	32 (11.7)	1 (0.4)
	Alopecia[*]	40 (14.6)	0
	Photosensitivity[*]	11 (4.0)	1 (0.4)
	Dermatitis acneiform[*]	12 (4.4)	0
	PPES	17 (6.2)	0
	Erythema[*]	22 (8.0)	0
	Panniculitis[*]	4 (1.5)	0
Musculoskeletal and connective tissue disorders	Arthralgia[*]	74 (27.0)	2 (0.7)
	Muscular disorders/ Myalgia [h]	71 (25.9)	2 (0.7)
	Back pain	30 (10.9)	2 (0.7)
	Pain in extremity	29 (10.6)	4 (1.5)
	Rhabdomyolysis	1 (0.4)	1 (0.4)
Renal and urinary disorders	Renal failure[*]	9 (3.3)	6 (2.2)

System Organ Class	Adverse reaction	Frequency All grades n (%)	Frequency Grades 3/4 n (%)
General disorders and administration site conditions	Pyrexia*	47 (17.2)	8 (2.9)
	Peripheral oedema [i]	42 (15.3)	3 (1.1)
	Fatigue*	120 (43.8)	8 (2.9)
Investigations	Blood creatine phosphokinase increased	74 (27.0)	16 (5.8)
	Transaminase increased*	43 (15.7)	15 (5.5)
	Gamma-glutamyl transferase increased*	40 (14.6)	23 (8.4)
	Blood creatinine increased*	17 (6.2)	2 (0.7)
	Blood alkaline phosphatase increased	20 (7.3)	2 (0.7)
	Amylase increased	9 (3.3)	4 (1.5)
	Lipase increased	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 and hypersensitivity vasculitis and urticaria

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

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

[e] includes haemorrhage at various sites including cerebral haemorrhage

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

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

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

[i] includes fluid retention, peripheral oedema, localised oedema.

Description of selected adverse reactions

Cutaneous squamous cell carcinoma

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

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 6.6% (18/274) 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. The median time to onset of the first event of RPED (all grades) was 1.5 month (range 0.03 to 17.5 months). RPED was generally reversible. Visual impairment, including vision blurred and reduced visual acuity, occurred in 21.5 % (59/274) of patients. Visual impairment was generally reversible.
Uveitis was reported when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Left ventricular dysfunction

In the pooled Combo 450 population, LVD was reported in 8.4% (23/274) of patients. Grade 3 events occurred in 1.1% (3/274) of patients. LVD led to treatment discontinuation in 0.4% (1/274) of patients and led to dose interruptions or dose reductions in 6.6% (18/274) of patients.

The median time to first occurrence of LVD (any grade) was 4.4 months (range 0.03 to 21.3 months) in patients who developed an LVEF below 50%. The mean LVEF value dropped by 5.9% in the pooled Combo 450 population from a mean of 63.9 % at baseline to 58.1%. LVD was generally reversible following dose reduction or dose interruption.

Haemorrhage

Haemorrhagic events have been observed in 17.9% (49/274) of patients in the pooled Combo 450 population. Most of these cases 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 for all patients.

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

Hypertension

New onset elevated blood pressure or worsening of pre-existing hypertension were reported in 11.7% (32/274) of patients treated with the Combo 450 mg. Hypertension related adverse events were reported as Grade 3 in 5.5% (15/274) of patients including hypertensive crisis (0.4% (1/274). Hypertension led to dose interruption or adjustment in 2.9% of patients. Hypertensive adverse reactions required additional therapy in 8.0 % (22/274) of patients.

Venous thromboembolism

In the pooled Combo 450 population, VTE occurred in 4.7% (13/274) of patients, including 2.2% (6/274) of patients who developed PE. VTE was reported as Grade 1 or 2 in 3.6% (10/274) of patients and Grade 3 or 4 in 1.1% (3/274) of patients. VTE led to dose interruptions or dose modifications in 1.1% (3/274) patients and to additional therapy in 4.7% (13/274) of patients.

Pancreatitis

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

Dermatological reactions

Rash

In the pooled Combo 450 mg 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.

Palmar-plantar erythrodysaesthesia syndrome

Palmar-plantar erythrodysaesthesia syndrome (PPES) was reported when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Acneiform dermatitis

In the pooled Combo 450 population, acneiform dermatitis occurred in 4.4% (12/274) of patients with no grade 3/4 events and no event led to treatment discontinuation. Dose modification was reported in 0.7% (2/274) of patients.

Photosensitivity

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

Facial paresis

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

CK elevation/Rhabdomyolysis

In the pooled Combo 450 population, mostly mild asymptomatic blood CK elevation was reported in 27.0% (748/274) of patients. The incidence of Grade 3 or 4 adverse events was 5.8% (16/274). The median time to onset of the first event was 2.7 months (range 0.5 to 17.5 months).

Rhabdomyolysis was reported in 0.4% (1/274) of patients treated with encorafenib in combination with binimetinib. In this patient, rhabdomyolysis was observed with concomitant symptomatic Grade 4 CK elevation.

Renal dysfunction

Blood creatinine elevation and renal failure occurred when binimetinib was used in combination with encorafenib (see section 4.8 *Adverse effects (undesirable effects)* of encorafenib PI).

Liver laboratory abnormalities

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

- ALT: 13.1 % (36/274) overall - Grade 3-4: 4.7 % (13/274)
- AST: 9.5 % (26/274) overall - Grade 3-4: 2.2 % (6/274)
- GGT: 14.6 % (40/274) overall - Grade 3-4: 8.4 % (23/274)
- 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) of patients had 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) 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 3 summarises adverse events (AEs) occurring at an incidence of ≥ 10% (all grades) or at an incidence of ≥ 2% incidence (grades 3 or 4) and reported in Part 1 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 3: Treatment-emergent adverse events occurring very commonly (≥10% any grade or ≥2 % grades 3 or 4) in patients receiving Combo 450 mg, Enco 300 mg or vemurafenib in Part 1 of study CMEK162B2301

	Combo 450mg QD N=192 n (%)		**Enco 300mg QD 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 creatine phosphokinase 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)
Gamma-glutamyltransferase 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

	Combo 450mg QD N=192 n (%)		Enco 300mg QD N=192 n (%)		Vemurafenib N=186 n (%)	
Grade	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Pain in extremity	22 (11.5)	2 (1.0)	43 (22.4)	2 (1.0)	26 (14.0)	2 (1.1)
Alanine aminotransferase 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)
Aspartate aminotransferase 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)
Palmar-plantar erythrodysaesthesia syndrome	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)

	Combo 450mg QD N=192 n (%)		Enco 300mg QD N=192 n (%)		Vemurafenib N=186 n (%)	
Grade	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Sunburn	0	0	1 (0.5)	0	19 (10.2)	1 (0.5)

A patient ais counted once within each preferred term.
Preferred terms are sorted in descending order of frequency in the 'Combo 450mg QD' column.
MedDRA Version 19.0 was used in 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 -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 proportion 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

The highest dose of binimetinib evaluated as single agent in clinical trials was 80 mg administered orally twice daily and was associated with ocular (chorioretinopathy) and skin toxicities (dermatitis acneiform).

In clinical trials of binimetinib in combination with encorafenib, one case of accidental overdose was reported. In this case, a subject took an overdose of 135 mg (9 tablets of binimetinib). No overdose of encorafenib was taken and no adverse events were reported.

Treatment of overdose
There is no specific treatment of overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Since binimetinib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with binimetinib.

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: L01EE03

Binimetinib is an ATP-uncompetitive reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation. In a cell free system, binimetinib inhibits MEK1 and MEK2 with the half maximal inhibitory (IC_{50})'s in the 12-46 nM. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. *In vitro*, binimetinib inhibits MEK-dependant phosphorylation of ERK in human BRAF-mutant melanoma cell lines, significantly inhibiting proliferation and viability of these cell lines. *In vivo*, binimetinib has been evaluated for its ability to inhibit phosphorylation of ERK and tumour growth in xenograft models in nude mice. Additionally, binimetinib has shown significant anti-tumour activity in BRAF-mutant xenograft models, including melanoma. Overall, binimetinib has demonstrated activity against MEK1 and MEK2 enzymes and possesses anti-proliferative activity *in vitro* and *in vivo*.

In non-clinical studies, the combination of binimetinib and encorafenib 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 BRAFV600E 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 BRAFV600E mutant human melanoma xenografts in mice.

Cardiac electrophysiology

In the safety analysis of pooled studies of encorafenib 450 mg once daily in combination with 45 mg binimetinib twice daily, 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* of encorafenib PI).

Clinical trials

BRAF V600 Mutant Unresectable or Metastatic Melanoma

The safety and efficacy of binimetinib in combination with encorafenib 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 included in the study were randomised to receive binimetinib 45 mg orally twice daily plus encorafenib 450 mg orally once 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), 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 – 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 with encorafenib 300 mg and 6.2 months in patients 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 4 and Figure 1 summarise the PFS and other efficacy results based on central review of the data by the BIRC.

Table 4: Progression-free survival and confirmed overall response results, cut-off date: 19 May 2016 (independent central review)

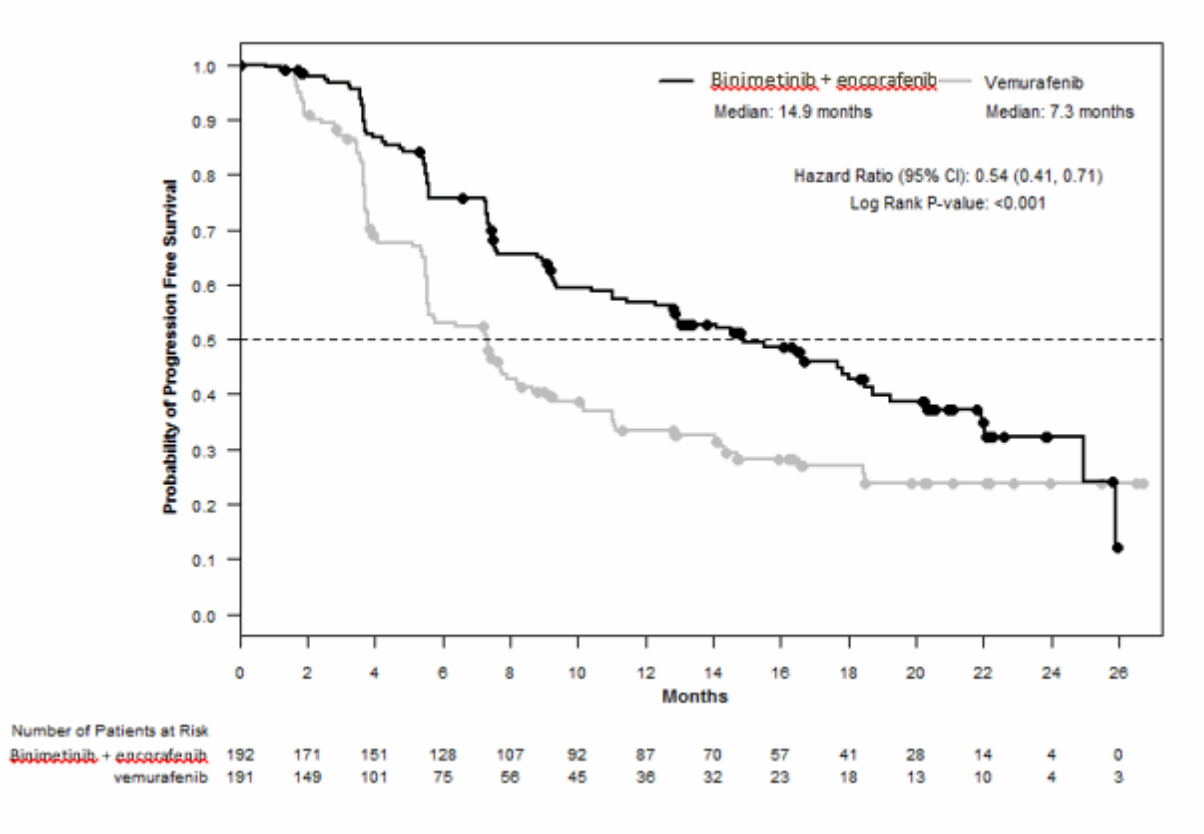
	Binimetinib and encorafenib N = 192 (Combo 450)	**Encorafenib N = 194 (Enco 300)**	**Vemurafenib N = 191 (Vem)**
PFS			
Number of events (progressive disease (PD)) (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	7.3 (5.6, 8.2)
HR[a] (95% CI) (vs. Vem) P value (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 (%)	121 (63.0)	98 (50.5)	77 (40.3)
(95% CI)	(55.8, 69.9)	(43.3 , 57.8)	(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 (%)	177 (92.2)	163 (84.0)	156 (81.7)
(95% CI)	(87.4, 95.6)	(78.1 , 88.9)	(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); NE = not estimable. PFS = progression-free survival.

[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 5.

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

	Binimetinib and encorafenib N = 192 (Combo 450)	**Encorafenib N = 194 (Enco 300)**	**Vemurafenib N = 191 (Vem)**
PFS			
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 (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); NE = not estimable. PFS = progression-free survival.

[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 assessment 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 independent central assessment 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 assessment showed consistent results.

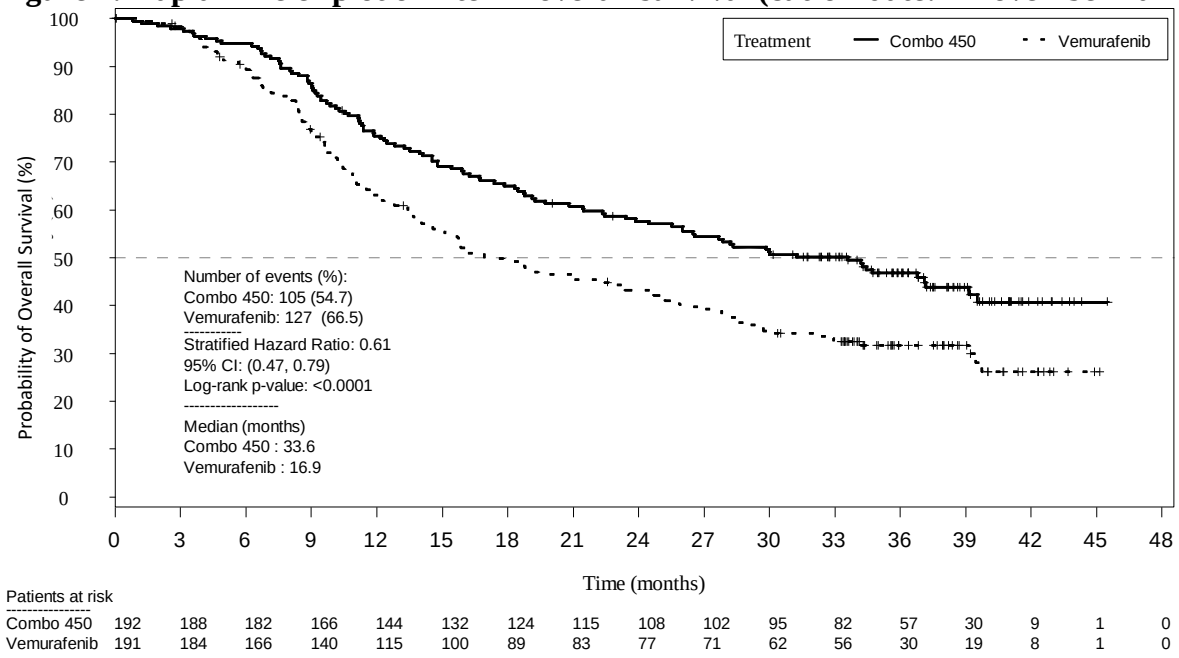
An interim OS analysis of study CMEK162B2301 Part 1, performed at the cut-off date of 07 November 2017, demonstrated a statistically significant improvement in OS for Combo 450 compared with vemurafenib (HR 0.61, 95% CI: 0.47, 0.79, [see **Table 6** and **Figure 2**]).
A similar proportion of patients in each treatment arm received subsequent treatment with checkpoint inhibitors, mainly pembrolizumab, nivolumab and ipilimumab (34.4% Combo 450 arm, 36.1% Enco 300 arm, 39.8% vemurafenib arm).

Table 6: Overall survival interim results (cut-off date: 7 November 2017)

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

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 Organization 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.

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of binimetinib were studied in healthy subjects and patients with solid tumours and advanced and unresectable or metastatic cutaneous melanoma. After repeated twice-daily dosing concomitantly with encorafenib, steady state concentrations were reached within 15 days with no major accumulation. The mean (CV %) $C_{max,ss}$ was 654 ng/mL (34.7 %) and mean AUC_{ss} was 2.35 ug.h/mL (28.0 %) in combination with encorafenib as estimated by population PK modelling. Binimetinib pharmacokinetics have been shown to be approximately dose-linear.

Absorption
After oral administration, binimetinib is rapidly absorbed with a median T_{max} of 1.5 hours. Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, at least 50% of the binimetinib dose was absorbed. Administration of a single 45 mg dose of binimetinib with a high-fat, high-calorie meal decreased the maximum binimetinib concentration (C_{max}) by 17%, while the area under the concentration –time curve (AUC) was unchanged. A drug interaction study in healthy subjects indicated that the extent of binimetinib exposure is not altered in the presence of a gastric pH-altering agent (rabeprazole).

Distribution
Binimetinib is 97.2% bound to human plasma proteins *in vitro*. Binimetinib is distributed to a greater extent in plasma than blood. In humans, the blood-to-plasma ratio is 0.718.

Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, the apparent volume of distribution (Vz/F) of binimetinib is 374 L.

Metabolism

Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, the primary biotransformation pathways of binimetinib observed in humans include glucuronidation, N-dealkylation, amide hydrolysis and loss of ethane-diol from the side chain. The maximum contribution of direct glucuronidation to the clearance of binimetinib was estimated to have been 61.2%. Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, approximately 60% of circulating radioactivity AUC in plasma was attributable to binimetinib. *In vitro*, CYP1A2 and CYP2C19 catalyses the formation of the active metabolite, which represents < 20% of the binimetinib exposure clinically.

Excretion

Following a single oral dose of 45 mg [^{14}C] binimetinib in healthy subjects, a mean of 62.3% of the radioactivity was eliminated in the faeces while 31.4% was eliminated in urine. In urine, 6.5% of the radioactivity was excreted as binimetinib. The mean (CV %) apparent clearance (CL/F) of binimetinib was 28.2 L/h (17.5%). The median (range) binimetinib terminal half-life ($T_{1/2}$) was 8.66 h (8.10 to 13.6 h).

Special populations

Hepatic impairment

As binimetinib is primarily metabolised and eliminated via the liver, patients with moderate to severe hepatic impairment may have increased exposure. Results from a dedicated clinical study with binimetinib only indicate similar exposures in patients with mild impairment (Child Pugh Class A) and subjects with normal liver function. A two-fold increase in exposure (AUC) was observed in patients with moderate (Child Pugh Class B) and severe (Child Pugh Class C) hepatic impairment (see section 4.2 *Dose and Method of Administration*). This increase expends to three-fold in both moderate and severe hepatic impairment when considering unbound binimetinib exposure (see section 4.2 *Dose and Method of Administration*).

The effects of hepatic impairment on the pharmacokinetics of binimetinib in combination with encorafenib have not been evaluated clinically.

Gilbert's syndrome

Binimetinib has not been evaluated in patients with Gilbert's disease. The main route of hepatic transformation of binimetinib being glucoronidation, the decision to treat should be made by the treating physician taking into account the individual benefit-risk.

Renal impairment

Binimetinib undergoes minimal renal elimination. Results from a dedicated clinical trial showed that patients with severe renal impairment (eGFR ≤29 mL/min/1.73 m^2), had a 29% increase in exposure (AUC_{inf}), a 21% increase in C_{max}, and a 22% decrease in CL/F compared

to matching healthy subjects. These differences were within the variability observed for these parameters in both cohorts of this study (25% to 49%) and the variability previously observed in patient clinical trials, hence these differences are unlikely to be clinically relevant (see section 4.2 *Dose and Method of Administration*).

The effects of renal impairment on the pharmacokinetics of binimetinib in combination with encorafenib have not been evaluated clinically.

Age/body weight
Based on a population PK analysis, age or body weight do not have a clinically important effect on the systemic exposure of binimetinib.

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

Paediatric use
The pharmacokinetics of binimetinib have not been established in children and adolescents below the age of 18 years.

Gender
Based on a population PK analysis, the pharmacokinetics of binimetinib were similar in males as compared with females.

Race
There are insufficient data to evaluate potential differences of race or ethnicity on binimetinib pharmacokinetics.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity
Binimetinib was negative for genotoxicity *in vitro* (reverse mutation in *Salmonella typhimurium* and *E coli* and forward mutation in mouse L5178Y $TK^{+/-}$ lymphoma cells) and *in vivo* (mouse micronucleus assay).

Carcinogenicity
Carcinogenic potential of binimetinib was not evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

The binimetinib drug product is an immediate release film-coated tablet for oral administration. Each tablet contains 15 mg binimetinib. The tablets also contain the excipients: lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate in the tablet core; and polyvinyl alcohol, macrogol 3350, titanium dioxide, purified talc, iron oxide yellow and iron oxide black in the film coating.

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 30C.

6.5. NATURE AND CONTENTS OF CONTAINER

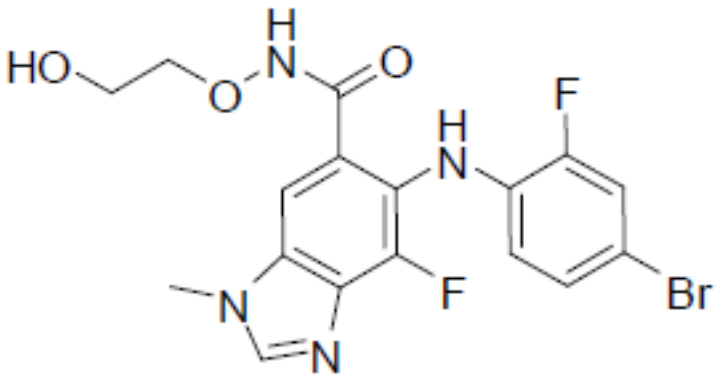
Container type: PVC/PVDC/Aluminium blister containing 12 tablets.
Each pack contains 84 tablets.

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
606143-89-9

Chemical name
5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-*N*-(2-hydroxyethoxy)- 1-methyl-1*H*-benzimidazole-6-carboxamide

Binimetinib is a white to slightly yellow powder with the molecular formula $C_{17}H_{15}BrF_2N_4O_3$ and a molecular weight of 441.23. At 37°C, binimetinib is slightly soluble (0.1 to 1%) at pH 1.0, very slightly soluble (0.01 to 0.1%) at pH 2.0 and insoluble between pH 4.5 and 7.5. Binimetinib is very slightly soluble (1.6%) in polyethylene glycol, slightly soluble in acetone, acetonitrile, propylene glycol, ethanol and methanol; and very slightly soluble in isopropyl alcohol and n-octanol. Its dissociation constants (pKa) are 2.5 and 8.11. Binimetinib is non-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

10 November 2021

Summary table of changes

Section changed	Summary of new information
5.1	ATC code updated to current ATC code
8	Pierre Fabre address updated