Encorafenib and Binimetinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with advanced (unresectable or metastatic) melanoma with a BRAF V600 mutation.	C43	00563a	01/05/2019 CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Encorafenib and binimetinib are administered daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Encorafenib	450mg daily	PO	Continuous
Binimetinib	45mg twice daily 12 hours apart	PO	Continuous
Encorafenib is available as 75mg capsules, binimetinib is available as 15mg tablets.			
Encorafenib capsules are to be swallowed whole with water. They may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided. Binimetinib tablets are to be swallowed whole with water. They may be taken with or without food.			
Missed doses If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose. 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 In case of vomiting after administration of encorafenib or binimetinib, the patient should not take an additional dose and should take the next scheduled dose.			

ELIGIBILITY:

- Indications as above
- BRAF V600 mutation as demonstrated by a validated test method
- ECOG status 0-1

USE with CAUTION:

Carefully consider benefits and risks before administering encorafenib to patients with a prior or concurrent cancer associated with RAS mutations.

EXCLUSIONS:

- Hypersensitivity to encorafenib, binimetinib or any of the excipients
- Prior therapy with a BRAF inhibitor and/or a MEK inhibitor
- Impaired cardiovascular function or clinically significant cardiovascular disease
- Impairment of gastrointestinal function
- Pregnancy/lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Creatinine Kinase (CK) and creatinine
- Blood Pressure
- ECG
- LVEF by echocardiogram or MUGA
- Dermatologic evaluation for other skin cancer

Regular tests:

- FBC, renal and liver profile monthly
- CK and creatinine levels monthly for the first 6 months of treatment and then as clinically indicated
- ECG: at initiation and at the end of the first 4 weeks and then every 12 weeks and after dose modification(prior to each cycle)
- LVEF - by echocardiogram or MUGA every 3 months or more frequently as clinically indicated
- Dermatologic evaluation every 60 days (assess for other skin cancers and new primary melanoma) and for up to 6 months following discontinuation of treatment
- Head and neck examination every 3 months
- Chest CT every 6 months

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation.

Renal and Hepatic Impairment:

Table 1: Recommended dose modification of encorafenib and binimetinib in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment	
Encorafenib	No dose adjustment is required for patients with mild or moderate renal impairment based on a population pharmacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential need for dose adjustment cannot be determined. Encorafenib should be used with caution in patients with severe renal impairment.	Patients with mild to severe hepatic impairment may have increased encorafenib exposure. 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.	
Binimetinib	No dose adjustment is recommended for patients with renal impairment.	Mild (Child-Pugh A)	No dose adjustment
		Moderate (Child Pugh B)	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.
		severe (Child-Pugh C)	

Recommended dose level reductions are provided in Table 2 below.

Table 2: Recommended dose modifications for encorafenib and binimetinib

Dose level	Encorafenib dose	Binimetinib Dose
Starting dose	450mg once daily	45mg twice daily
1st dose reduction	300mg once daily	30mg twice daily
2nd dose reduction	200mg once daily	Not recommended
Subsequent modification	There are limited data for dose reduction to 100mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100mg once daily.	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 of binimetinib is under effective management, dose 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.		
Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. **If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption as encorafenib is not well-tolerated at the dose of 450 mg as a single agent.**		

- Dose modifications recommendations in case of adverse reactions are presented below in Tables 3 and 4.
  - 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 reductions 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. Dose modifications are necessary for binimetinib only (adverse reactions primarily related to binimetinib) for the following: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation and rhabdomyolysis, and venous thromboembolism (VTE).
  - If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption (see Tables 2 and 3) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent.
  - If binimetinib is permanently discontinued, encorafenib should be discontinued.
  - If encorafenib is temporarily interrupted, binimetinib should be interrupted.
  - If encorafenib is permanently discontinued, then binimetinib should be discontinued.

Table 3: Recommended dose modifications for encorafenib and binimetinib for selected adverse reactions

	Binimetinib	**Encorafenib**
Cutaneous reactions		
Grade 2	Maintain binimetinib. If rash worsens or does not improve within 2 weeks with treatment, binimetinib should be withheld until improved to Grade 0 or 1 and then resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent Grade 2.	Maintain encorafenib. If rash worsens or does not improve within 2 weeks with treatment, encorafenib should be withheld until Grade 0 or 1 and then resumed at the same dose.
Grade 3	Binimetinib and encorafenib should be withheld until improved to Grade 0 or 1 and resumed at the same dose if first occurrence or resumed at a reduced dose if recurrent Grade 3.	
Grade 4	Permanently discontinue	
Ocular events		
Symptomatic retinal pigment epithelial detachments (RPED) (Grade 2 or 3)	Consider ophthalmology evaluation including optical coherence tomography if concern of RPED Binimetinib should be withheld for up to 2 weeks and ophthalmic monitoring should be repeated including visual acuity assessment. • If improved to Grade 0 or 1, binimetinib should be resumed 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 (Grade 4)	Permanently discontinue	
Retinal vein occlusion (RVO)	Permanently discontinue	
Uveitis including iritis and iridocyclitis		
Grade 1-3		If Grade 1 or 2 uveitis does not respond to specific (e.g. topical) ocular therapy or for Grade 3 uveitis, encorafenib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. If uveitis is Grade 1 and it improves to Grade 0, then treatment should be resumed at the same dose. If uveitis is Grade 2 or 3 and it improves to Grade 0 or 1, then treatment should be resumed at a reduced dose. If not improved within 6 weeks, ophthalmic monitoring should be repeated and encorafenib should be permanently discontinued.
Grade 4		Encorafenib should be permanently discontinued and a follow up with ophthalmologic monitoring should be performed.
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)	LVEF should be evaluated every 2 weeks. • If asymptomatic: Binimetinib should be withheld for up to 4 weeks. Binimetinib should be resumed at a reduced dose if all of the following are present within 4 weeks: o LVEF is at or above the LLN o Absolute decrease from baseline is 10 % or less. • If the LVEF does not recover within 4 weeks, binimetinib should be permanently discontinued.	
Grade 3 or 4 LVEF decrease or symptomatic left ventricular	Permanently discontinue LVEF should be evaluated every 2 weeks until recovery.	

dysfunction (LVD)		
QTc Prolongation QTcF > 500 ms and change ≤ 60 ms from pre-treatment value		Encorafenib should be withheld Encorafenib should be resumed at a reduced dose when QTcF ≤500 ms. Encorafenib should be discontinued if more than one recurrence
QTcF>500 ms and increased by >60 ms from pre-treatment values		Encorafenib should be permanently discontinued
Rhabdomyolysis/Creatine phosphokinase (CK) elevation		
Grade 3 (CK > 5 – 10x upper limit of normal (ULN)) asymptomatic	Binimetinib dose should be maintained and it should be ensured that patient is adequately hydrated.	
Grade 4 (CK > 10x ULN) asymptomatic	Binimetinib should be withheld until improved to Grade 0 or 1. It should be ensured that patient has adequate hydration.	
Grade 3 or grade 4 (CK > 5x ULN) with muscle symptoms or renal impairment	Binimetinib should be withheld until improved to Grade 0 or 1. • If resolved within 4 weeks, binimetinib should be resumed at a reduced dose, or • Binimetinib should be permanently discontinued	
Venous thromboembolism (VTE		
Uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) ≤ Grade 3	Binimetinib should be withheld. • If improved to Grade 0 or 1, binimetinib should be resumed at a reduced dose, or • If not improved, binimetinib should be permanently discontinued.	
Grade 4 PE	**Permanently discontinue**	
Liver laboratory abnormalities		
Grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x – ≤ 5x upper limit of normal (ULN)	Maintain dose. If no improvement within 2 weeks, binimetinib should be withheld until improved to Grade 0 or 1 or to baseline levels, and then resumed at the same dose.	Maintain dose. If no improvement within 4 weeks, encorafenib should be withheld until improved to Grade 0 or 1 or to pretreatment/baseline levels and then resumed at the same dose.
First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN	Binimetinib and encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, binimetinib and encorafenib should be resumed at reduced dose. • If not improved, binimetinib and encorafenib should be permanently discontinued.	
First occurrence of Grade 4 (AST or ALT	Binimetinib and encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, binimetinib and encorafenib	

> 20 ULN)	should be resumed at a reduced dose level, or • If not improved, binimetinib and encorafenib should be permanently discontinued. Or, binimetinib and 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 binimetinib and encorafenib	
Recurrent Grade 4 (AST or ALT > 20 ULN)	Permanently discontinue	
Interstitial lung disease (ILD)/pneumonitis		
Grade 2	Binimetinib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1, binimetinib should be resumed at reduced dose, or • If not resolved within 4 weeks, binimetinib should be permanently discontinued.	
Grade 3 or Grade 4	Permanently discontinue	
Palmar-plantar erythrodysaesthesia syndrome (PPES)		
Grade 2		Encorafenib should be maintained and supportive measures such as topical therapy should be instituted. If not improved despite supportive therapy within 2 weeks, encorafenib should be withheld until improved to Grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.
Grade 3		Encorafenib should be withheld, supportive measures such as topical therapy should be instituted, and the patient should be reassessed weekly. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to Grade 0 or 1.

Table 4: Recommended dose modifications for binimetinib and encorafenib for other adverse reactions

Severity of adverse reaction	Encorafenib and Binimetinib
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Binimetinib and encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline level, binimetinib and encorafenib should be resumed at reduced dose, • If not improved, binimetinib and encorafenib should be permanently discontinued
First occurrence of Grade 4 adverse reactions	Binimetinib and encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or baseline levels, binimetinib and encorafenib should be resumed at a reduced dose level. • If not improved, binimetinib and encorafenib should be permanently discontinued. Or, Binimetinib and encorafenib should be permanently discontinued
Recurrent Grade 3 adverse reactions	Consider permanent discontinuation of binimetinib and encorafenib
Recurrent Grade 4 adverse reactions	Binimetinib and encorafenib should be permanently discontinued.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Encorafenib: Moderate to High **(Refer to local policy)**
Binimetinib: Moderate to High **(Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Women of childbearing potential must use effective contraception during treatment with binimetinib and encorafenib and for at least 1 month following the last dose. Encorafenib may decrease the 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.

Male patients should be informed of the potential risk for impaired spermatogenesis with implications for fertility and the potential for foetal harm if fathering a child

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Encorafenib and binimetinib: These medicinal products are subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Binimetinib in combination with encorafenib in patients who have progressed on a BRAF inhibitor** :There are limited data for use of the combination of binimetinib with encorafenib in patients who have progressed on a prior BRAF inhibitor given for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients.
- **Binimetinib in combination with encorafenib in patients with brain metastases** There are limited efficacy data with the combination of binimetinib and encorafenib in patients with a BRAF V600 mutant melanoma which have metastasised to the brain.
- **Left ventricular dysfunction (LVD**). The occurrence of LVEF decrease can be managed with treatment interruption, dose reduction or with treatment discontinuation (Table 3). 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.
- **Haemorrhage** : Haemorrhages, including major haemorrhagic events, can occur with encorafenib and binimetinib. The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ≥3 haemorrhagic events should be managed with dose interruption or treatment discontinuation (see Table 3 above) and as clinically indicated.
- **Ocular toxicities**: Ocular toxicities including uveitis, iritis and iridocyclitis can occur when encorafenib is administered. RPED has also been reported in patients treated with encorafenib in combination with binimetinib. Patients should be assessed at each visit for symptoms of new or worsening visual disturbance. If symptoms of new or worsening visual disturbances are identified, a prompt ophthalmologic examination is recommended. If, uveitis including iridocyclitis and iritis occurs during treatment, see Table 3. If during treatment patient develops RPED or RVO, see Table 3 for guidance. 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. Therefore, binimetinib should be used with caution in these patients
- **CK elevation and rhabdomyolysis:** Asymptomatic CK elevations are seen in patients treated with binimetinib and, rhabdomyolysis was uncommonly reported. Special attention should be paid to 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 Table 3 above).
- **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 3).

- **Venous thromboembolism (VTE)**: VTE can occur when binimetinib is administered . Binimetinib should be used with caution in patients who are at risk for, or who have a history of VTE. If during treatment patient develops VTE or pulmonary embolism, it should be managed with dose interruption, reduction or treatment discontinuation (see Table 3).
- **Pneumonitis/Interstitial lung disease**: This 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 3 above). Binimetinib should be permanently discontinued in patients diagnosed with treatment related pneumonitis or ILD
- **QT prolongation**: QT Prolongation has been observed in patients treated with BRAF-inhibitors. 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 before treatment initiation and during treatment.
- **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), as well as kerathoacanthoma has been observed in patients treated with binimetinib in combination with encorafenib. New primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib. Dermatologic evaluations should be performed prior to initiation of therapy with encorafenib in combination with binimetinib, every 2 months while on therapy and for up to 6 months following discontinuation of the combination. Suspicious skin lesions should be managed with dermatological excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Encorafenib and binimetinib should be continued without any dose modification.

  Non-cutaneous malignancies:

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

DRUG INTERACTIONS:

- 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. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.
- Encorafenib is both an inhibitor and inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g., hormonal contraceptives) may result in increased toxicity or loss of efficacy of these agents. Agents that are CYP3A4 substrates should be co-administered with caution.
- Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 (e.g. raltegravir, atorvastatin, dolutegravir) may have increased exposure and should be therefore administered with caution.
- Encorafenib potentially inhibits a number of transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 (such as furosemide, penicillin) or agents that are substrates of the hepatic transporters OATP1B1, OATP1B3, OCT1 (such as atorvastatin, bosentan) or substrates of BCRP (such as methotrexate, rosuvastatin) may have increased exposure and should be therefore co-administered with caution.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	25/06/2019		Dr Fergal Kelleher
2	04/02/2021	Baseline and regular tests updated	Dr Fergal Kelleher
3	23/06/2021	Reviewed. Added to treatment table and dose modifications. Amended emetogenic potential.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.