Cobimetinib and Vemurafenib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Cobimetinib and vemurafenib in combination are indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	C43	00373a	CDS (01/04/2018)

*This applies to post 2012 indications only

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.

Cobimetinib is taken once daily for 21 consecutive days (Days 1 to 21-treatment period); followed by a 7-day break (Days 22 to 28-treatment break).

Vemurafenib is taken twice daily continuously (1 cycle = 28 days).

Treatment is continued until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route		Cycle
1-21	Cobimetinib	60mg once daily	PO Swallow whole with water.	May be taken with or without food	Every 28 days
1-28	Vemurafenib	960mg BD	PO Swallow whole with water.	May be taken with or without food Consistent intake of both daily doses on an empty stomach should be avoided	Every 28 days
Missed doses If a dose of cobimetinib is missed, it can be taken up to 12 hours prior to the next dose to maintain the once-daily regimen. If a dose of vemurafenib is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. **Both doses should not be taken at the same time**.					
Vomiting In case of vomiting after administration of cobimetinib or vemurafenib, the patient should **not** take an additional dose. The next prescribed dose should be taken at the usual time.					
Cobimetinib is commonly available as 20mg film coated tablets. Vemurafenib is commonly available as 240mg tablets.					

ELIGIBILITY:

- Indication as above
- BRAF V600 mutation as demonstrated by a validated test method
- ECOG status 0-1
- LVEF > 50%

EXCLUSIONS:

- Hypersensitivity to cobimetinib, vemurafenib or any of the excipients
- Wild type BRAF malignant melanoma
- Previous treatment failure with a BRAF inhibitor
- QT-interval longer than 500 milliseconds (Treatment with vemurafanib not recommended)
- Concomitant treatment with drugs known to prolong QT interval
- Uncontrolled electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Uncontrolled hypertension
- Breast feeding
- Pregnancy

USE WITH CAUTION:

- Vemurafenib should be used with caution when given before, during or following radiation treatment. Prescribers should be aware of the risk of potentiation of radiation toxicity

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH
- Cardiac Function : ECG and LVEF

Regular tests:

- FBC, renal and liver profile prior to each cycle
- LDH prior to each cycle
- ECG: every 4 weeks (prior to each cycle) for the first 12 weeks, then every 12 weeks and after dose modification
- All patients restarting treatment with a dose reduction of cobimetinib should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated

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 decision on whether to reduce the dose for either or both treatments should be based on the prescriber's assessment of individual patient safety or tolerability
- Dose modification of cobimetinib is independent of vemurafenib dose modification
- If doses of cobimetinib or vemurafenib are omitted for toxicity, these doses should not be replaced
- Once the dose of cobimetinib or vemurafemib has been reduced, it should not be increased at a later time

Dose Level Reductions for cobimetinib and vemurafenib

Table 1: Dose Level Reductions for cobimetinib and vemurafenib

Dose Level	Cobimetinib	Vemurafenib
-1	40mg daily	720mg BD
-2	20mg daily	480mg BD
Further dose reduction indicated	Permanently discontinue	Permanently discontinue

Renal and Hepatic Impairment:

Table 2: Recommended dose modifications in patients with renal or hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="2">Hepatic impairment</th></tr>
<tr><td rowspan="2">Cobimetinib</td><td colspan="2">No dose adjustment is needed</td><td colspan="2" rowspan="2">No dose adjustment is needed</td></tr>
<tr><td>Haemodialysis</td><td>No need for dose adjustment is expected</td></tr>
<tr><td>Vemurafenib</td><td>CrCl mL/min</td><td>Dose</td><td></td><td>Dose</td></tr>
<tr><td rowspan="3"></td><td>≥30mL/min</td><td>No dose adjustment is needed</td><td>Mild / Moderate</td><td>No dose adjustment is needed</td></tr>
<tr><td><30mL/min</td><td>No need for dose adjustment is expected</td><td rowspan="2">Severe</td><td rowspan="2">No need for dose adjustment is expected, monitor liver biochemistry twice a week</td></tr>
<tr><td>Haemodialysis</td><td>No need for dose adjustment is expected</td></tr>
</table>

Non-haematological toxicity:

Table 3: Recommended dose modifications for cobimetinib and vemurafenib

Grade (CTC-AE)*	Recommended dose of cobimetinib	Recommended dose of vemurafenib
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at a dose of 60 mg once daily (3 tablets)	Maintain vemurafenib at a dose of 960 mg twice daily
Grade 2 (intolerable) or Grade 3 1st occurrence	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily (2 tablets)	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg once daily (1 tablet)	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily.
3rd occurrence	Consider permanent discontinuation	Discontinue permanently
Grade 4 1st occurrence	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily (2 tablets)	Discontinue permanently or interrupt vemurafenib treatment until Grade 0-1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily)
2nd occurrence	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg once daily (1 tablet)	
2nd occurrence or persistence of any grade 4 after 1st dose reduction		Discontinue permanently
3rd occurrence	Consider permanent discontinuation	
*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)		

Cobimetinib and Left ventricular dysfunction :

- Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to cobimetinib and do not improve after temporary interruption.
- Table 4 shows the recommended dose modifications for cobimetinib in patients with left ventricular ejection fraction (LVEF) decrease from baseline.

Table 4: Recommended dose modifications for cobimetinib in patients with LVEF decrease from baseline

Patient	LVEF value	Recommended cobimetinib dose modification	LVEF following treatment break	Recommended cobimetinib daily dose
Asymptomatic	≥ 50% or (40-49% and <10% absolute decrease from baseline)	Continue at current dose	N/A	N/A
	<40% or (40-49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	<10% absolute decrease from baseline	1st occurrence: 40mg 2nd occurrence: 20mg 3rd occurrence : permanent discontinuation
			<40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	N/A	Interrupt treatment for 4 weeks	Asymptomatic and <10% absolute decrease from baseline	1st occurrence: 40mg 2nd occurrence: 20mg 3rd occurrence : permanent discontinuation
			Asymptomatic and <40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

Table 5: Recommended dose modifications for cobimetinib and vemurafenib

Haemorrhage **Grade 4 or cerebral haemorrhage**	Cobimetinib treatment should be interrupted and permanently discontinued for haemorrhage events attributed to cobimetinib..
Grade 3	Cobimetinib treatment should be interrupted during evaluation to avoid any potential contribution to the event. There is no data on the effectiveness of cobimetinib dose modification for haemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. Vemurafenib dosing can be continued when cobimetinib treatment is interrupted, if clinically indicated.
Rhabdomyolysis or symptomatic CPK elevations	Cobimetinib treatment should be interrupted. If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, treatment with cobimetinib should be permanently discontinued. If severity is improved by at least one grade within 4 weeks, cobimetinib could be restarted at a dose reduced by 20 mg, if clinically indicated. Patients should be closely monitored. Vemurafenib dosing can be continued when cobimetinib treatment is modified**.**
Asymptomatic CPK elevations **Grade ≤3** **Grade 4**:	After rhabdomyolysis has been ruled out, cobimetinib dosing does not need to be modified**.** Cobimetinib treatment should be interrupted. If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, cobimetinib treatment should be permanently discontinued. If CPK improves to Grade ≤3 within 4 weeks, cobimetinib could be restarted, if clinically indicated, at a dose reduced by 20 mg and the patient should be closely monitored. Vemurafenib dosing can be continued when cobimetinib treatment is modified.

Liver laboratory abnormalities **Grade 1 and 2**	Cobimetinib and vemurafenib should be continued at the prescribed dose.
Grade 3	Cobimetinib should be continued at the prescribed dose. Hold vemurafenib. Upon resolution of LFT to Grade ≤ 1,resume vemurafenib at 1 lower dose level
Grade 4	Cobimetinib treatment and vemurafenib treatment should be interrupted. If liver laboratory abnormalities improve to Grade ≤1 within 4 weeks, Cobimetinib should be restarted at a dose reduced by 1 dose level and vemurafenib should be decreased by 2 dose levels. Cobimetinib treatment and vemurafenib treatment should be discontinued if liver laboratory abnormalities do not resolve to Grade ≤1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur after initial improvement
Photosensitivity **Grade≤ 2 (tolerable)**	Manage with best supportive care
Grade 2 (intolerable) or Grade ≥3 photosensitivity:	Cobimetinib and vemurafenib should be interrupted until resolution to Grade ≤1. Treatment can be restarted with no change in cobimetinib dose. Vemurafenib dosing should be reduced as clinically appropriate (see Table 3).
Rash	Dose of cobinetinib and/or vemurafenib may be interrupted and/or reduced as clinically indicated. Additionally for;
Grade ≤2 (tolerable) rash	Manage with best supportive care
Grade 2 (intolerable) or Grade ≥3 acneiform rash	General dose modification recommendations in Table 1 for cobimetinib should be followed. Vemurafenib dosing can be continued when cobimetinib treatment is modified (if clinically indicated).
Grade 2 (intolerable) or Grade ≥3 non-acneiform or maculopapular rash:	Cobimetinib dosing can be continued without modification if clinically indicated. Vemurafenib dosing may be either temporarily interrupted and/or reduced (see Table 3).
Diarrhoea **Grade ≤ 2**	No change in dosing of cobimetinib or vemurafenib. Manage with supportive care.
Grade ≥3 (despite supportive care) **1st occurrence**	Hold both cobimetinib and vemurafenib until resolved to Grade≤ 1.
Recurrent	Reduce the dose of both cobimetinib and vemurafenib
QT prolongation	If during treatment the QTc exceeds 500 msec, see Table 6 below for dose modifications for vemurafenib. No dose modification of cobimetinib is required when taken in combination with vemurafenib

Table 6: Dose modification schedule of vemurafenib based on prolongation of the QT interval

QTc value	Discontinue	Recommended dose modification
QTc>500 ms at baseline		Treatment not recommended.
QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values	Discontinue permanently.	
1st occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms		Temporarily interrupt treatment until QTc < 500ms. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms		Temporarily interrupt treatment until QTc < 500ms. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Discontinue permanently.	

(CTC-AE v4.0).

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting -Available on the NCCP website

Cobimetinib: Minimal to Low (**Refer to local policy).**
Vemurafenib: Minimal to Low (**Refer to local policy).**

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

Not usually required.

OTHER SUPPORTIVE CARE:

- Cobimetinib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with cobimetinib 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.
- Women of childbearing potential should be advised to use two effective contraceptive methods, such as a condom or other barrier method (with spermicide, if available) during treatment with cobimetinib and for at least three months following treatment discontinuation

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.
- **This medicinal product, Cobimetinib, is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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2. Larkin J, Ascierto P et al. Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. NEJM, 2014;371(20):1867-1876.
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Cobimetinib (Cotellic®) Summary of Product Characteristics. Accessed September 2024. Available at: https://www.medicines.ie/medicines/cotellic-20-mg-film-coated-tablets-31729/spc#tabs
6. Vemurafenib (Zelboraf®) Summary of Product Characteristics. Accessed September 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	20/03/2018		Prof Fergal Kelleher
2	01/05/2020	Reviewed. Updated emetogenic potential section.	Prof Fergal Kelleher
3	05/11/2024	Reviewed. Updated exclusions section. Updated renal and hepatic dose modifications to align with Giraud et al 2023. Updated adverse events drug interactions, regimen specific complications in line with NCCP standardisation.	Prof Fergal Kelleher

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.