# Cobimetinib and Vemurafenib Therapy

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | 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) |

## 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<br>Swallow whole with water. | May be taken with or without food | Every 28 days |
| 1-28 | Vemurafenib | 960mg BD | PO<br>Swallow whole with water. | May be taken with or without food<br>Consistent intake of both daily doses on an empty stomach should be avoided | Every 28 days |
| **Missed doses**<br>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.<br>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.<br>**Both doses should not be taken at the same time**. | | | | | |
| **Vomiting**<br>In case of vomiting after administration of cobimetinib or vemurafenib, the patient should **not** take an additional dose.<br>The next prescribed dose should be taken at the usual time. | | | | | |
| Cobimetinib is available as 20mg film coated tablets<br>Vemurafenib is available as 240mg tablets. | | | | | |

## ELIGIBILTY:

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



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## 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

## 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.



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## 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>Hepatic impairment</th></tr>
<tr><td rowspan="3">Cobimetinib</td><td>Mild</td><td rowspan="2">No dose adjustment recommended</td><td rowspan="3">No dose adjustment is recommended<br>Patients with severe hepatic impairment may have increased plasma concentrations of unbound cobimetinib compared to patients with normal hepatic function.<br>Liver laboratory abnormalities can occur with cobimetinib and caution should be used in patients with any degree of hepatic impairment.</td></tr>
<tr><td>Moderate</td></tr>
<tr><td>Severe</td><td>No data available<br>Use with caution</td></tr>
<tr><td>Vemurafenib</td><td colspan="2">Limited data are available<br>A risk for increased exposure in patients with severe renal impairment cannot be excluded.<br>Patients with severe renal impairment should be closely monitored</td><td>Limited data are available.<br><br>As vemurafenib is cleared by the liver, patients with moderate to severe hepatic impairment may have increased exposure and should be closely monitored</td></tr>
</table>



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**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.<br>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**<br>1st occurrence | Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily (2 tablets) | Interrupt treatment until grade 0 – 1.<br>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.<br>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**<br>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.<br>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 3 shows the recommended dose modifications for cobimetinib in patients with left ventricular ejection fraction (LVEF) decrease from baseline.



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**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<br>2nd occurrence: 20mg<br>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<br>2nd occurrence: 20mg<br>3rd occurrence : permanent discontinuation |
| | | | Asymptomatic and <40% (or ≥ 10% absolute decrease from baseline) | Permanent discontinuation |
| | | | Symptomatic regardless of LVEF | Permanent discontinuation |



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**Table 5: Recommended dose modifications for cobimetinib and vemurafenib**

| | |
|---|---|
| **Haemorrhage**<br>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.<br>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.<br>If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, treatment with cobimetinib should be permanently discontinued.<br>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.<br>Vemurafenib dosing can be continued when cobimetinib treatment is modified**.** |
| **Asymptomatic CPK elevations**<br>**Grade ≤3**<br>**Grade 4**: | After rhabdomyolysis has been ruled out, cobimetinib dosing does not need to be modified**.**<br>Cobimetinib treatment should be interrupted.<br>If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, cobimetinib treatment should be permanently discontinued.<br>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.<br>Vemurafenib dosing can be continued when cobimetinib treatment is modified. |



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| | |
|---|---|
| **Liver laboratory abnormalities**<br>**Grade 1 and 2** | Cobimetinib and vemurafenib should be continued at the prescribed dose. |
| **Grade 3** | Cobimetinib should be continued at the prescribed dose.<br>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.<br><br>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**<br>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.<br>Treatment can be restarted with no change in cobimetinib dose.<br>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.<br>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**<br>Grade ≤ 2 | No change in dosing of cobimetinib or vemurafenib. Manage with supportive care. |
| Grade ≥3 ( despite supportive care)<br>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.<br>No dose modification of cobimetinib is required when taken in combination with vemurafenib |



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**Table 5: 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:

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

### 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 / REGIMEN SPECIFIC COMPLICATIONS

***Cobimetinib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.*** *The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details*.

**Cobimetinib**

- **Severe Haemorrhage:** Severe haemorrhagic events, including intracranial and gastrointestinal tract bleeds have been reported in patients receiving cobimetinib in clinical trials and post-marketing. Cobimetinib should be used with caution when given to patients with additional risk factors for bleeding, such as brain metastases, and/or concomitant medications that increase the risk of bleeding (such as antiplatelet and anticoagulant therapy).
- **Rhabdomyolysis and Creatine Phosphokinase (CPK) Elevations:** Rhabdomyolysis and CPK elevations have been reported in patients receiving cobimetinib clinical trials and post-marketing. Baseline



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serum CPK and creatinine levels should be measured before starting treatment, and then monitored monthly during treatment or as clinically indicated. If serum CPK is elevated, check for signs and symptoms of rhabdomyolysis or other causes.

- **Serous retinopathy:** Cases of serous retinopathy have been reported in patients treated with cobimetinib. For patients reporting new or worsening visual disturbances, an ophthalmologic examination is recommended. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation (see Table 3)
- **Lactose intolerance:** This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, congenital lactase deficiency or glucose-galactose malabsorption should consult with their physician and discuss whether the benefits outweigh the risks on an individual basis.

**Vemurafenib**

- **Risk Factors for Torsade de Points:** Treat with caution in patients with risk factors for Torsade de Points.
- **Cutaneous Squamous Cell Carcinoma (cuSCC):** Dose modification or interruption is not recommended. Cases of cuSCC are typically managed with simple excision, and patients are able to continue treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of vemurafenib or until initiation of another anti-neoplastic therapy. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.
- **Other Cancers:** Skin cancers (Squamous cell carcinoma (SCC) and Kerathocantomas (KAs)) have been reported at an increased frequency and there have been 2 reports (as of August 2012) of oral SCC cancers. There are theoretical concerns of lung cancer.
- **Pancreatitis:** Unexplained abdominal pain should be promptly investigated (including measurement of serum amylase and lipase). Patients should be closely monitored when re-starting vemurafenib after an e**pisode of panc**reatitis
- **Photosensitivity**: Mild to severe photosensitivity has been reported. All patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF 30 or higher**)** when outdoors to help protect against sunburn. For photosensitivity, grade 2 (intolerable) or greater adverse events, dose modifications are recommended (see Table 3).
- **Hepatic Impairment:** Vemurafenib is primarily eliminated by the liver. Patients with mild hepatic impairment due to liver metastases without hyperbilirubinaemia may be monitored according to the general recommendations. There are only very limited data available in patients with moderate to severe hepatic impairment. Patients with moderate to severe hepatic impairment may have increased exposure. Thus close monitoring is warranted especially after the first few weeks of treatment as accumulation may occur over an extended period of time (several weeks).
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions, including anaphylaxis have been reported. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalized rash, erythema or hypotension. Treatment with vemurafenib should be permanently discontinued**.**
- **Ophthalmologic:** Vemurafenib treatment-related serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions and refer to Ophthalmologist if clinically indicated.
- **Radiation Related Injuries:** Severe cases of radiation related injuries, some with fatal outcome, have been reported in patients treated with radiation either before, during, or following treatment with vemurafenib. Vemurafenib should be used with caution when given before, during, or following radiation treatment.



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## DRUG INTERACTIONS:

- Concurrent use of strong CYP3A inhibitors during treatment with cobimetinib should be avoided. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with cobimetinib. If concomitant use with a strong or moderate CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety and dose modifications applied if clinically indicated
- Cobimetinib is a substrate of P-glycoprotein (P-gp). Concomitant administration of P-gp inhibitors such as ciclosporin and verapamil may have the potential to increase plasma concentrations of cobimetinib.
- QT-prolonging Medications: Vemurafenib causes QT prolongation. Concomitant use of QT-prolonging medications (e.g. amiodarone, sotalol, haloperidol, amitriptyline, methadone, fluconazole, erythromycin, ciprofloxacin, ondansetron, formoterol, quinidine, tacrolimus) should be avoided if possible.
- Vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor and a CYP3A4 inducer. Caution should be exercised when used with medications predominantly metabolized by CYP1A2, CYP2D6 and CYP3A4.
- Vemurafenib is a substrate of CYP3A4. Concomitant use of moderate and strong CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John's Wort) should be avoided.
- Co-administration of vemurafenib resulted in a 20% increase in AUC of warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

| | |
|---|---|
| Cobimetinib | L01XE38 |
| Vemurafenib | L01XE15 |

## REFERENCES:


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| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 20/03/2018 | | Dr Fergal Kelleher |
| 2 | 01/05/2020 | Reviewed.<br>Updated emetogenic potential section | Dr Fergal Kelleher |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.



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