**Dabrafenib for Unresectable or Metastatic Melanoma**

**Indication:** Treatment of unresectable or metastatic melanoma with BRAF V600 mutation and intolerance to vemurafenib.

**National Cancer Drug Fund criteria to be met:**
- Advanced melanoma
- BRAF V600E mutation
- PS 0 or 1
- Severe intolerance to vemurafenib requiring discontinuation within 2 months of initiating vemurafenib
- Absence of disease progression whilst on full dose of vemurafenib
- No other previous systemic therapy for the treatment of melanoma other than vemurafenib.

Cancer drug fund application and approval is required prior to starting treatment.

**Notes:** Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities (including magnesium), or a long QT syndrome (QTc >500ms) or who are taking medicinal products known to prolong the QT interval.

**Regimen details:** Dabrafenib 150mg PO Twice daily

**Administration:** Available as 75mg and 50mg hard capsules. Swallow whole with water on an empty stomach, either 1 hour before, or 2 hours after a meal, and approximately 12 hours apart. Do not chew or crush.

**Frequency:** Prescribed every 28 days - continued until disease progression or unacceptable toxicity

**Anti-emetics:** Minimal emetogenicity Follow local anti-emetic policy

**Regular investigations:**
- FBC Baseline and prior each cycle
- U&Es (incl Mg) Baseline and prior each cycle
- LFTs (incl. AST, ALT, Alk P) Baseline and prior each cycle
- ECG Baseline and after 1 month, then periodically as indicated or after dose modification

**Toxicities:** Headache, pyrexia, chills, cough, arthralgia, myalgia, fatigue, nausea, vomiting, rash, pruritis, hyperkeratosis, PPE, uveitis, diarrhoea, asthenia, renal failure, pancreatitis, QT prolongation, LVEF decrease, hypophosphataemia, hyperglycaemia, anorexia, alopecia, constipation, risk of secondary carcinoma (cutaneous or non-cutaneous squamous cell carcinoma)
DOSE MODIFICATIONS

Haematological toxicity
Discuss any haematological toxicity and dose reductions with the consultant

Non-Haematological Toxicity

Renal Impairment
Dose adjustments not required in mild or moderate renal impairment. There are no clinical data in patients with severe renal impairment, use with caution, no dose adjustments can be recommended.

Hepatic Impairment
No adjustment is required for patients with mild hepatic impairment.
There is no clinical data in patients with moderate to severe hepatic impairment, use with caution, no dose adjustments can be recommended. Additional ECG monitoring is required in patients with moderate/severe hepatic impairment; monthly for first 3 months, then 3 monthly or as clinically indicated.

Dose modifications for other toxicities

Pyrexia
Onset of non-serious febrile events typically occur within the first month of therapy. Dabrafenib should be interrupted if the patient's temperature is ≥38.5°C. Patients should be evaluated for signs and symptoms of infection. Dabrafenib may be restarted once the fever resolves with appropriate prophylaxis using paracetamol or non-steroidal anti-inflammatory agents. If fever is associated with other severe signs or symptoms, dabrafenib should be interrupted and restarted at a dose reduction as clinically appropriate.

Dose modifications based on the grade of any adverse reactions (except QT interval prolongation and cutaneous squamous cell carcinoma – see below)

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>Dabrafenib dose</th>
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<tbody>
<tr>
<td>Grade 1 or Grade 2</td>
<td>Continue and monitor</td>
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<tr>
<td>Grade 2 (intolerable)</td>
<td>Interrupt treatment until resolved to Grade 0-1 then</td>
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<tr>
<td>OR</td>
<td>First occurrence: Reduce to 100mg BD</td>
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<tr>
<td>Grade 3</td>
<td>Second occurrence: Reduce to 75mg BD</td>
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<td></td>
<td>Third occurrence: Reduce to 50mg BD</td>
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<tr>
<td>Grade 4</td>
<td>Discontinue permanently</td>
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<tr>
<td>OR</td>
<td>Discuss with consultant - interrupt therapy until resolved to Grade 0-1 then reduce to 100mg BD. If Grade 4 toxicity recurs, discontinue permanently.</td>
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</table>
**QT interval prolongation**

<table>
<thead>
<tr>
<th>QTc Value</th>
<th>Dabrafenib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt; 500 ms at baseline</td>
<td>Treatment not recommended</td>
</tr>
<tr>
<td>QTc values &gt; 500 ms and &lt; 60 ms change from pre-treatment baseline values</td>
<td>Interrupt treatment until QTc reduced to &lt; 500 ms&lt;br&gt;Correct electrolyte imbalances (incl. Mg)&lt;br&gt;Assess for cardiac risk factors&lt;br&gt;  - First occurrence: Reduce to 100mg BD&lt;br&gt;  - Second occurrence: Reduce to 75mg BD&lt;br&gt;  - Third occurrence: Reduce to 50mg BD</td>
</tr>
<tr>
<td>QTc values &gt; 500 ms <strong>AND</strong> &gt; 60 ms change from pre-treatment baseline values</td>
<td>Discontinue permanently</td>
</tr>
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**Cutaneous Squamous Cell Carcinoma (CuSCC)**

It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy, and monthly while on dabrafenib, and continue for 6 months after treatment for CuSCC. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. Dabrafenib should be continued without any dose adjustment. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.

Comments: To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan.

Drug interactions:
- Caution with a history of QT interval prolongation or relevant pre-existing cardiac disease, and concurrent antiarrhythmics or other medicines that may prolong the QT interval.
- Concurrent use of CYP2C8 and CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates, St John’s Wort) can decrease dabrafenib plasma concentration and reduce efficacy.
- Concurrent use of CYP2C8 and CYP3A4 inhibitors (e.g. amiodarone, cyclosporine, ketoconazole, itraconazole, voriconazole, posaconazole, erythromycin, clarithromycin, ritonavir, diltiazem, verapamil, quinidine, grapefruit juice) can increase dabrafenib plasma concentration and increase toxicity.
- Medicinal products such as proton pump inhibitors that inhibit gastric acid secretion (increase gastric pH) may decrease solubility of dabrafenib and reduce bioavailability.
- Exercise caution and consider additional INR (International Normalized Ratio) monitoring when dabrafenib is used concomitantly with warfarin and at discontinuation of dabrafenib – decreased warfarin exposure
- Concomitant administration of dabrafenib with digoxin may result in decreased digoxin exposure – additional monitoring is recommended when dabrafenib is used concomitantly with digoxin and at discontinuation of dabrafenib.