Dabrafenib (skin)

Indication
BRAF V600 mutation-positive unresectable or metastatic melanoma in patients with a WHO performance status of 0-2.

(NICE TA321)

ICD-10 codes
Codes with a prefix C43

Regimen details

Day	Drug	Dose	Route
1-28*	Dabrafenib	150mg BD	PO

*Continuously until unacceptable toxicity or disease progression

Cycle frequency
As above

Number of cycles
Continuous until disease progression or unacceptable toxicity.

Administration
Dabrafenib is available as 75 and 50mg capsules.
Dabrafenib should be taken at least one hour before or two hours after food. Doses should be taken 12 hours apart, swallowed whole with water, not chewed or crushed.
Grapefruit and grapefruit juice should be **avoided** whilst taking dabrafenib.

If a dose is missed it should be taken if it is more than six hours until the next dose is due. If within six hours the dose should be missed and the next dose taken as planned. Doses should be taken at similar times every day. If the patient vomits an additional dose should not be taken but the next dose taken as usual.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential.

Additional supportive medication
Emollients if required.
Antiemetics if required.

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days

ECG (QTc < 500ms)

Investigations – pre subsequent cycles

Patients should be reviewed every 4 weeks for the first 3 months.

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	96hours
LFTs	96 hours

ECG (QTc <500ms and <60ms increase from baseline). ECG should be monitored before treatment, after the first month and after any dose modifications. Further monitoring is recommended in patients with moderate to severe hepatic impairment (see hepatic impairment section).

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
QTc	<500ms and <60ms increase from baseline
Creatinine clearance (CrCl)	≥ 30ml/min
AST/ALT	≤ 2.5 x ULN (or <5 x ULN if liver metastases)

Dose modifications

Dose modifications should be made as per the table below:

Dose level	**Dosing schedule**
First reduction	100mg BD
Second reduction	75mg BD
Third reduction	50mg BD

- **Haematological toxicity**

See below for management of pyrexia.

- **Renal impairment**

Limited data available. No dose reduction necessary for mild to moderate renal impairment. Use with caution and closely monitor if severe renal impairment.

- **Hepatic impairment**

No dose modification is required for mild hepatic impairment. There is no data in moderate to severe hepatic impairment. As dabrafenib is metabolised primarily by the liver use with caution.

Additional ECG monitoring is required in patients with moderate or severe hepatic impairment; monthly for the first 3 months, then 3 monthly or as clinically indicated.

- **Other toxicities**

Dose modification for any adverse drug reaction based on toxicity grading:

Toxicity grade	Dabrafenib dose modification
Grade 1 or 2 (tolerable)	Continue treatment and monitor
Grade 2 (intolerable) or Grade 3	Interrupt treatment until ≤ Grade 1. Resume with dose reduction of one level.
Grade 4	Discontinue or interrupt treatment until ≤ Grade 1. Resume with dose reduction of one level.

QT prolongation:
If the QTc exceeds 500 msec, dabrafenib treatment should be temporarily interrupted, electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur once the QTc decreases below 500 msec with a one level dose reduction.

Permanent discontinuation of dabrafenib treatment is recommended if the QTc increase meets values of both > 500 msec and > 60 msec change from pre-treatment values.

Pyrexia:
Dabrafenib should be interrupted if the patient's temperature is ≥ 38.5°C. Patients should be evaluated for signs and symptoms of infection. Dabrafenib can be restarted once the fever resolves with appropriate prophylaxis using non-steroidal anti-inflammatory medicinal products or paracetamol. If fever is associated with other severe signs or symptoms, dabrafenib should be restarted at a reduced dose once fever resolves and as clinically appropriate.

Skin tumours:
Cases of skin squamous cell carcinomas should be treated with surgical excision. No dose adjustment is required. Dermatological evaluation should continue for 6 months after the cessation of dabrafenib.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Cutaneous squamous cell carcinoma
Non-cutaneous squamous cell carcinoma
New primary melanoma
QT prolongation
Pancreatitis
Hypersensitivity reactions
Ophthalmic reactions, including uveitis

- **Frequently occurring side effects**

Pyrexia
Fatigue
Headache
Cough
Arthralgia, myalgia
Hyperkeratosis
Nausea and vomiting
Diarrhoea
Alopecia
Raised LFTs

- **Other side effects**

Hypophosphataemia
Hyperglycaemia

Significant drug interactions – for full details consult product literature/ reference texts

Medication which prolong the QT interval: Concomitant use not recommended as dabrafenib may prolong QT interval.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to dabrafenib.

Inhibitors of CYP3A4 (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir): use with caution

Coumarin anticoagulants, e.g. Warfarin: monitor INR closely.

Contraceptive pill: efficacy may be reduced.

Digoxin: concomitant use may reduce digoxin levels.

There is a theoretical risk that drugs which raise gastric pH may decrease dabrafenib bioavailability.

Dabrafenib can interact with many medicinal products eliminated through metabolism or active transport. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. Please see the SPC for a full list of potential medicinal interactions.

Additional comments

References

- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 321 accessed 17 December 2014 via www.nice.org.uk
- Summary of Product Characteristics – Dabrafenib (GSK) accessed 17 December 2014 via www.medicines.org.uk
- Hauschild, A et al; Dabrafenib in BRAF mutated metastatic melanoma. Lancet 2012; 380: 358 - 365

Written/reviewed by: Dr T Tillett (Consultant Oncologist, Royal United Hospital, Bath)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

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