Dabrafenib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	C43	00237a	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.

Dabrafenib is administered daily until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Dabrafenib	150 mg twice daily	PO	Continuous
Capsules should be swallowed whole with water. They should NOT be chewed or crushed and should NOT be mixed with food or liquids. Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal.			
If a dose is missed, it should not be taken if it is < 6 hours until next dose. Dabrafenib should be taken at similar times each day, leaving an interval of approximately 12 hours between doses.			

ELIGIBILITY:

- Indications as above
- BRAF V600 mutation as demonstrated by a validated test method
- ECOG status 0-2
- Sequential treatment may be considered where patients are intolerant to a prescribed BRAF inhibitor and are subsequently changed to an alternative

EXCLUSIONS:

- Hypersensitivity to dabrafenib or any of the excipients
- Long QT syndrome-interval longer than 500 milliseconds
- Concomitant treatment with drugs known to prolong QT interval
- Uncontrolled electrolyte abnormalities (e.g., hypokalaemia, hypomagnesaemia, hypocalcaemia)
- Uncontrolled hypertension
- Pregnancy* (Reference **Drug Interactions below**: Dabrafenib reduces efficacy of hormonal contraceptives)
- Breast feeding
- Wild type BRAF malignant melanoma
- Treatment failure with a BRAF inhibitor

USE WITH CAUTION:

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

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- Dermatologic evaluation for other skin cancer.

Regular tests:

- FBC, renal and liver profile monthly.
- ECG: every 4 weeks (prior to each cycle) for the first 12 weeks, then every 12 weeks and after dose modification.
- Dermatologic evaluation monthly (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.

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.
- Dose modifications are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma.
- Therapy should be interrupted if patient's temperature is ≥ 38.5^{0}C and they should be evaluated for signs and symptoms of infection.
- No dose reductions are recommended for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib therapy until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level (see Table 1).

Table 1: Dose reduction steps for dabrafenib.

Dose Level	Dabrafenib Dose
Full Dose	150mg BD
1st Reduction	100mg BD
2nd Reduction	75mg BD
3rd Reduction	50mg BD
Dose adjustment for dabrafenib below 50mg BD is not recommended	

Renal and Hepatic Impairment:

Table 2: Dose modification of dabrafenib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
No dose adjustment is required for patients with mild or moderate renal impairment. There are no clinical data in subjects with severe renal impairment.	No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in subjects with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites and patients with moderate to severe hepatic impairment may have increased exposure. Dabrafenib should be used with caution in patients with moderate or severe hepatic impairment.

Management of adverse events:

Table 3: Dose Modification of dabrafenib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 1 or 2 (Tolerable)	Continue treatment and monitor as clinically indicated
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy
Grade 4	Discontinue permanently or interrupt therapy until grade 0-1 and reduce by one dose level when resuming therapy.
When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The dabrafenib dose should not exceed 150 mg twice daily	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: None usually required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Pyrexia**: Patients with serious non-infectious febrile events have responded well to dose interruption and/or dose reduction and supportive care. Therapy with 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.

- **Cutaneous Squamous Cell Carcinoma (cuSCC):** Cases of cuSCC have been reported in patients treated with dabrafenib. They should be managed by dermatological excision and dabrafenib treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their physician if new lesions develop. It is recommended that skin examination be performed prior to initiation of therapy with dabrafenib and monthly throughout treatment and for up to six months after treatment for cuSCC or until initiation of another anti-neoplastic therapy.
- **New primary melanoma:** Cases have been identified within the first 5 months of therapy. They were managed with excision and did not require treatment modification. Monitoring for skin lesions should occur as described for cuSCC.
- **Non-cutaneous secondary/recurrent malignancy:** Prior to initiation of treatment patients should undergo a head and neck examination with minimally visual inspection of oral mucosa and lymph node palpation, as well as chest/abdomen CT scan. During treatment patients should be monitored as clinically appropriate which may include a head and neck examination every 3 months and a chest/abdomen CT scan every 6 months. Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated. Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.
- **Renal failure:** Patients should be routinely monitored for serum creatinine while on therapy. If creatinine increases, dabrafenib may need to be interrupted as clinically appropriate. Dabrafenib has not been studied in patients with renal insufficiency (defined as creatinine > 1.5 x ULN) therefore caution should be used in this setting.
- **Visual impairment**: Ophthalmologic reactions, including uveitis and iritis have been reported. Patients should be routinely monitored for visual signs and symptoms (such as change in vision, photophobia and eye pain) while on therapy.
- **Pancreatitis:** Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.

DRUG INTERACTIONS:

- Potent inducers of CYP3A4 and CYP2C8 may reduce the efficacy of dabrafenib.
- *Dabrafenib may decrease the efficacy of hormonal contraceptives. Women of childbearing potential should use an alternative effective method of contraception during therapy and for 2 weeks following discontinuation.
- Concomitant administration with warfarin may result in decreased warfarin exposure. Additional INR monitoring is required during treatment and at discontinuation of dabrafenib.
- Concomitant administration with digoxin may result in decreased digoxin exposure. Additional monitoring of digoxin is required during treatment and at discontinuation of dabrafenib.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Ascierto P, Minor D et al. Phase II Trial (BREAK-2) of the BRAF Inhibitor Dabrafenib (GSK2118436) in Patients with Metastatic Melanoma. J Clin Oncol 2013; 31:3205-3211.
2. Hauschild A, Grab JJ et al. Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet, 2012: 380;358365.
3. Tafinlar ®Summary of Product Characteristics. Accessed Jan 2021 Available at https://www.ema.europa.eu/en/documents/product-information/tafinlar-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. 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

Version	Date	Amendment	Approved By
1	10/1/2015		Dr Jennifer Westrup, Dr Fergal Kelleher
2	11/01/2017	Review-Updated ECOG status, dose modifications re uveitis and third dose reduction as per SmPC Removed QT prolongation section from Adverse Events as per updated SmPC	Prof Maccon Keane
3	16/01/2019	Updated to new NCCP template Updated treatment table and adverse reactions	Prof Maccon Keane
4	15/04/2019	Removed black triangle status as per SmPC update	Prof Maccon Keane
5	22/01/2021	Amended eligibility, regular tests, emetogenic potential and drug interactions.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.