DABRAFENIB

Monotherapy for BRAF V600 mutation positive unresectable or metastatic melanoma (NICE approved Oct 2014)

Drug/Dosage:	Dabrafenib	150mg po	twice daily continuous therapy

Administration: Available as 50mg and 75mg capsules (patients to be started on 3 x 50mg capsules per dose, to minimise wastage in the event of a dose reduction)
Each dose should be taken at least 1 hour before, or at least 2 hours after, a meal.
Capsules should be swallowed whole with water; do not chew or crush, and do not mix with food or liquids, due to chemical instability of dabrafenib.
Grapefruit and grapefruit juice should be avoided while on dabrafenib.
Doses should be taken approximately 12 hours apart. If a dose is missed, it should not be taken if it is less than 6 hours until the next dose.

Frequency: continue for as long as there is clinical benefit, or unacceptable toxicity.

Main Toxicities: adverse drug reactions reported in ≥ 15 % patients: hyperkeratosis (skin thickening), headache, pyrexia, arthralgia, nausea, vomiting, papilloma, alopecia, rash, fatigue

Anti- emetics: mildly emetogenic

Regular:	FBC	every 4 weeks for 3 months, then every 3 months
Investigations:	LFTs and U&Es	every 4 weeks for 3 months, then every 3 months
	LDH	every 4 weeks for 3 months, then whenever a blood test is done

Clinical examination and orthogonal measurement +/- photography of accessible lesions at baseline, then monthly throughout treatment (see Comments)
Whole body PET or CT neck, chest, abdomen and pelvis (NCAP) baseline, then CT NCAP every 3 months

Comments: Any suspicious skin lesions should be excised, sent for evaluation, and managed according to local practice. In patients who develop cutaneous squamous cell carcinoma or new primary melanoma, treatment may continue without dose adjustment.

Interactions: Concomitant use of potent enzyme inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) should be avoided, as this may increase the risk of therapeutic failure.

Concomitant use of strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin) may increase the risk of dabrafenib-associated toxicity.

Dabrafenib is a CYP3A4 enzyme inducer. Interactions with medicines which are eliminated via CYP3A4 metabolism are expected. Onset of induction is likely to be within 3 days of starting dabrafenib.
This is one of the most important enzymes involved in the metabolism of drugs, so it is not possible to provide a complete list of medicines eliminated via this pathway. Examples include fentanyl, clarithromycin, cabazitaxel, warfarin, anti-epileptics, calcium channel blockers, dexamethasone, levothyroxine, simvastatin. If in doubt, check with pharmacy.
If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed by monitoring of efficacy or plasma concentrations, these medicines should be avoided or used with caution.

Reason for Update: removed need to monitor QT	Approved by Consultant: Dr M Ajaz
Version: 3	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 2	Date: 28.3.17
Prepared by: S Taylor	Checked by: C Tucker

The efficacy of contraceptive pills metabolised by CYP3A4 may be decreased.

Theoretical risk that drugs which raise gastric pH may decrease dabrafenib bioavailability.

Dose Modifications The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation. N.B. Dose modifications below 50mg bd are not recommended.

Pyrexia: Therapy 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 paracetamol or non-steroidal anti-inflammatory agents.
If the fever is associated with other severe signs and symptoms (e.g. severe rigors, hypotension, acute renal insufficiency), dabrafenib should be interrupted and restarted with a dose reduction once the fever resolves, as clinically appropriate.

Dose modifications for any adverse drug reaction (except pyrexia) based on CTC grading:

Grade	Recommended Dose Modification
Grade 1 or 2 (tolerable)	Maintain dose level
Grade 2 (intolerable) or Grade 3	Interrupt until Grade 0 – 1, then • 1st occurrence: reduce to 100mg bd • 2nd occurrence: reduce to 75mg bd • 3rd occurrence: reduce to 50mg bd
Grade 4	Discontinue permanently *or* Interrupt until Grade 0 – 1, then reduce by one dose level, as above, when resuming therapy.

Hepatic Impairment: No dose adjustment is required for patients with mild hepatic impairment.
Hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites: use with caution in patients with moderate or severe hepatic impairment; there are no clinical data, and no dose adjustment can be recommended.

Renal Impairment: No dose adjustment is required for patients with mild or moderate renal impairment.
Use with caution in patients with severe renal impairment.

Reference: Hauschild, A et al; Lancet 2012; 380: 358 - 365