Indication	Monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days Continuous until progression of disease or unacceptable toxicity.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, LFT's and U&E's prior to each cycle for 3 months, then every 3 months thereafter. • Electrocardiogram (ECG) and electrolytes (including magnesium) must be monitored in all patients before treatment, after one month of treatment and after any dose modification. Patients with moderate to severe hepatic impairment should have monthly ECGs for the first 3 months of treatment. • A chest CT should be perfomed prior to treatment and every 6 months during treatment. • Cases of Cutaneous Squamous Cell Carcinoma (cuSCC) and Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC) have been reported in patients receiving vemurafenib. All patients should undergo dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy and for 6 months after. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. • **Hepatic impairment:** Patients with moderate to severe hepatic impairment should be closely monitored, d/w consultant. • **Renal impairment:** Patients with severe renal impairment should be closely monitored, d/w consultant. • **Management of adverse reactions and dose adjustments:** • Patients should avoid sun exposure and use SPF 30 or higher as routine. If dermatological side effects occur d/w consultant. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued. • Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions. • Vemurafenib can cause prolongation of the QT interval. Management of QT prolongation may require specific monitoring measures - see dose modification table 1. Use in patients with uncorrectable electrolyte abnormalities (including magnesium) or long QT syndrome or taking other medicines that lead to QT prolongation (e.g. amiodarone, sotalol, clarithromycin, quinidine, chloroquine) is not recommended. • **Dose Modification: See table 1 and table 2.** • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** • Avoid concomitant treatment with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin) or inducers (e.g. rifampicin, dexamethasone, phenytoin, St. John's Wort, carbamazepine). • Patients on warfarin should be closely monitored (INR). • Concomitant use of vemurafenib with agents metabolized by CYP1A2 with narrow therapeutic windows (e.g. agomelatine, alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine, theophylline) is not recommended. If co-administration cannot be avoided, exercise caution, as vemurafenib may increase plasma exposure of CYP1A2 substrate drugs. Dose reduction of the concomitant CYP1A2 substrate drug may be considered, if clinically indicated. • Concomitant use of vemurafenib with agents metabolized by CYP3A4 with narrow therapeutic windows (e.g. amiodarone, carbamazepine, ciclosporin, aminophylline) is not recommended.

	If co-administration cannot be avoided, it needs to be considered that vemurafenib may decrease plasma concentrations of CYP3A4 substrates and thereby their efficacy may be impaired. Dose adjustments for CYP3A4 substrates with narrow therapeutic window may be considered, if clinically indicated. The efficacy of contraceptive pills metabolised by CYP3A4 may be decreased. • Due to the long half-life of vemurafenib, the full inhibitory effect of vemurafenib on a concomitant medicinal product might not be observed before 8 days of vemurafenib treatment. After cessation of vemurafenib treatment, a washout of 8 days might be necessary to avoid an interaction with a subsequent treatment • Caution should be exercised when dosing vemurafenib concurrently with P-gp substrates (e.g. colchicine, dabigatran etexilate, aliskiren, digoxin, posaconazole); additional drug level monitoring and dose reduction of the concomitant medicinal product may be considered, if clinically indicated. • **Driving:** Patients should be aware that vemurafenib may affect their ability to drive or operate machinery. • **Missed dose:** If a dose is missed, it can be taken up to 4 hours prior to the next dose, otherwise the dose should be omitted. In case of vomiting after vemurafenib dose the patient should not take an additional dose and the next dose taken as scheduled. • **For oral self-administration:** refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	KMCC proforma SKI-003 V4 SPC accessed online 14.06.2023

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modification schedule for adverse reactions based on grade.

Grade	**Recommended dose modification**
Grade 1 or Grade 2 (tolerable)	Maintain dose of 960 mg twice daily.
1st occurrence of any Grade 2 (intolerable) or Grade 3	Interrupt treatment until grade 0 – 1. Resume dosing at 720mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of any grade 2 or 3 or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume dosing at 480mg twice daily (or discontinue permanently if the dose has already been lowered to 480mg twice daily).
3rd occurrence of any grade 2 or 3 or persistence after 2nd dose reduction	Discontinue permanently.
1st occurrence of any grade 4	Discontinue permanently or interrupt vemurafenib treatment until grade 0 – 1. Resume dosing at 480mg twice daily (or discontinue permanently if the dose has already been lowered to 480mg twice daily).
2nd occurrence of any grade 4 or persistence of any grade 4 after 1st dose reduction	Discontinue permanently.

Table 2 Dose modification schedule based on prolongation of QT interval

QTc value	Recommended dose modification
QTc >500ms 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 >500ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. 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 decreases below 500 ms. Electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. 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.

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**VEMURAFENIB**	**960mg**	PO	Twice daily as continuous treatment. Swallow tablets whole with water, do not crush or chew. The first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose should always be taken in the same manner i.e. either with or without a meal. Available as 240mg tablets – Dispense 4 x 56 per cycle
	Metoclopramide	10mg	PO	up to 3 times a day as required. Do not take for more than 5 days continuously. Dispense 28 tablets on cycle 1, then only if specified.