Vemurafenib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement Status*
Treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.	C43	00102a	CDS

*This applies to post 2012 indications only

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.

Vemurafenib is administered daily until disease progression or unacceptable toxicity develops (1 cycle = 28 days).

Drug	Dose	Route	Cycle
Vemurafenib	960mg twice daily	PO	Continuous
Take doses approximately 12 hours apart preferably with food. May be taken without food but taking both daily doses on an empty stomach should be avoided. Tablets should be swallowed whole with water. They should NOT be chewed or crushed.			
Missed Doses and Vomiting: If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time. In the case of vomiting after vemurafenib administration the patient should not take an additional dose of vemurafenib. The next prescribed dose should be taken at the usual time.			
Vemurafenib is commonly available as 240mg tablets.			

ELIGIBILITY:

- Indications as above
- BRAF V600 mutation as demonstrated by a validated test method
- ECOG status 0-2
- Adequate haematological, hepatic and renal function

EXCLUSIONS:

- Hypersensitivity to vemurafenib or to any of the excipients
- Concomitant treatment with any other anticancer therapy
- QT-interval longer than 500 milliseconds
- Pregnancy

CAUTION:

- When given before, during or following radiation treatment. Prescribers should be aware of the risk of potentiation of radiation toxicity.
- Uncontrolled electrolyte abnormalities (e.g. hypokalemia, hypomagnesemia, hypocalcemia)
- Wild type BRAF malignant melanoma

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG/QT interval evaluation for patients at risk
- Dermatologic evaluation for other skin cancer
- Chest CT scan (included with metastatic melanoma staging)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- ECG every 4 weeks (prior to each cycle) for the first 12 weeks, then every 12 weeks and after dose modification.
- Dermatologic evaluation: at week 8 (assess for other skin cancers and new primary melanoma); monitoring beyond 8 weeks can be performed by the oncologist or dermatologist every 12 weeks

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
- Management of adverse drug reactions or QTc prolongation may require dose reduction; temporary interruption and/or treatment discontinuation (see Tables 1 and 3 below).
- Dose reduction below 480 mg twice daily is not recommended
- In the event the patient develops Cutaneous Squamous Cell Carcinoma (cuSCC), it is recommended to continue the treatment without modifying the dose of vemurafenib.
- Dose escalation after dose reduction is generally not recommended unless under special circumstances (i.e. increased likelihood of clinical benefit for the dose increase and no safety concerns).

Table 1: Dose modification schedule based on the grade of any adverse events

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

*(CTC-AE v4.0).

Renal and Hepatic Impairment:

Table 2: Dose modification of vemurafenib renal and hepatic impairment

Renal impairment		**Hepatic impairment**	
CrCl (mL/min)		**Impairment level**	
≥ 30	No dose adjustment is needed	Mild and moderate	No dose adjustment is needed
< 30	No need for dose adjustment is expected	Severe	No need for dose adjustment is expected, monitor liver biochemistry twice a week.
Haemodialysis	No need for dose adjustment is expected		

Management of adverse events:

Table 3: Dose modification schedule based on prolongation of the QT interval

QTc value	Recommended dose modification
QTc>500 ms 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>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc < 500ms. 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 < 500ms. 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

(CTC-AE v4.0)

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

Vemurafenib : Minimal **(Refer to local policy).**

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Women of childbearing potential have to use effective contraception during treatment and for at least 6 months after treatment.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Chapman et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-16.
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3. Zelboraf (vemurafenib)-Important Safety Information from Roche Products (Ireland)Ltd. As approved by the HPRA Available at http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---zelboraf-(vemurafenib).pdf?sfvrsn=0
4. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
6. Zelboraf ® Summary of Product Characteristics. Last updated: 27/03/2024. Accessed December 2024 Available at: https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	07/03/13		Dr Paul Donnellan
2	01/03/15	Updated Disease Monitoring Section	Dr Maccon Keane
3	25/11/2015	Inserted Use with Caution section. Updated Treatment and Dose Modification Section (renal and liver impairment), Adverse Effects (potentiation of radiation toxicity and pancreatitis)	Dr Maccon Keane
4	06/12/2017	Updated with new NCCP template. Updated Adverse Reactions	Prof Maccon Keane
5	08/01/2020	Reviewed. Update of adverse events.	Prof Maccon Keane
6	24/02/2025	Regimen reviewed. Updated eligibility and exclusions section. Updated renal and hepatic dose modifications table to align with Giraud et al 2023. Updated other supportive care section. Regimen updated throughout in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.