Vemurafenib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.	C43	00102a	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.

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

Drug	Dose	Route	Cycle
Vemurafenib	960mg BD	PO (approximately 12 hours apart) preferably with food. May be taken without food but taking both daily doses on an empty stomach should be avoided. Swallow whole.	Continuous
Tablets should be swallowed whole with water. They should NOT be chewed or crushed			
Misse 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 available as 240mg tablets.			

ELIGIBILTY:

- Indications as above
- BRAF V600 mutation as demonstrated by a validated test method
- ECOG status 0-2
- Life expectancy of at least 3 months
- 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
- Uncontrolled electrolyte abnormalities (e.g. hypokalemia, hypomagnesemia, hypocalcemia)
- Uncontrolled hypertension
- Wild type BRAF malignant melanoma

Use with Caution:

- When given before, during or following radiation treatment. Prescribers should be aware of the risk of potentiation of radiation toxicity.

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)
- Smear test in women younger than 65 years old (if not done within 3 years and no hysterectomy; 65 years and older do not need smear test unless clinically indicated)

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.

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.

- 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

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
Limited data are available in patients with renal impairment. A risk for increased exposure in patients with severe renal impairment cannot be excluded. Patients with severe renal impairment should be closely monitored	Limited data are available in patients with hepatic impairment. As vemurafenib is cleared by the liver, patients with moderate to severe hepatic impairment may have increased exposure and should be closely monitored

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

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Risk Factors for Torsade de Points:** Treat with caution in patients with risk factors for Torsade de Points.
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions, including anaphylaxis have been reported. Severe hypersensitivity reactions may include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), generalized rash, erythema or hypotension. Treatment with vemurafenib should be permanently discontinued.
- **Dermatologic reactions**: Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens - Johnson syndrome a nd toxic epidermal necrolysis in the pivotal clinical trial. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with vemurafenib in the post-marketing setting. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued.
- **Cutaneous Squamous Cell Carcinoma (cuSCC):** Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with vemurafenib Dose modification or interruption is not recommended. Cases of cuSCC are typically managed with simple excision, and patients are able to continue treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of vemurafenib or

until initiation of another anti-neoplastic therapy. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.

- **Other Cancers:** Cases of non-cutaneous Squamous Cell carcinoma (non-cuSCC) and primary melanoma have been reported in clinical trials. Based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. Carefully consider benefits and risks before administering vemurafenib to patients with a prior or concurrent cancer associated with RAS mutation.
- **Pancreatitis:** Unexplained abdominal pain should be promptly investigated (including measurement of serum amylase and lipase). Patients should be closely monitored when re-starting vemurafenib after an episode of pancreatitis
- **Photosensitivity:** Mild to severe photosensitivity has been reported. All patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF 30 or higher) when outdoors to help protect against sunburn. For photosensitivity, grade 2 (intolerable) or greater adverse events, dose modifications are recommended (see Table 1).
- **Hepatic Impairment:** Vemurafenib is primarily eliminated by the liver. Patients with mild hepatic impairment due to liver metastases without hyperbilirubinaemia may be monitored according to the general recommendations. There are only very limited data available in patients with moderate to severe hepatic impairment. Patients with moderate to severe hepatic impairment may have increased exposure. Thus close monitoring is warranted especially after the first few weeks of treatment as accumulation may occur over an extended period of time (several weeks). In addition ECG monitoring every month during the first three months is recommended.
- **Radiation Related Injuries:** Severe cases of radiation related injuries, some with fatal outcome, have been reported in patients treated with radiation either before, during, or following treatment with vemurafenib. Most cases were cutaneous in nature but some cases involved visceral organs. Vemurafenib should be used with caution when given before, during, or following radiation treatment.
- **Ophthalmologic:** Vemurafenib treatment-related serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions and refer to Ophthalmologist if clinically indicated.
- **Dupuytren's contracture and plantar fascial fibromatosis:** Cases of Dupuytren's contracture and plantar fascial fibromatosis have been reported with vemurafenib. The majority of cases were mild to moderate, but severe, disabling cases of Dupuytren's contracture have also been reported. Events should be managed with dose reduction with treatment interruption or with treatment discontinuation.

DRUG INTERACTIONS:

- QT-prolonging Medications: Vemurafenib causes QT prolongation. Concomitant use of QT-prolonging medications (should be avoided if possible.
- Vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor and a CYP3A4 inducer. Caution should be exercised when used with medications predominantly metabolized by CYP1A2, CYP2D6 and CYP3A4.
- Vemurafenib may increase the plasma exposure of medicinal products that are P - gp substrates. Caution should be exercised, dose reduction and/or additional drug level monitoring for P- gp substrate medicinal products with narrow therapeutic index (e.g. may be considered if these medicinal products are used concomitantly with vemurafenib

- Vemurafenib is a substrate of CYP3A4. Caution should be exercised when used with strong CYP3A4 inhibitors or inducers (including St. John's Wort).
- Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.
- Current drug interaction databases should be consulted for more information

ATC CODE:

Vemurafenib L01XE15

REFERENCES:

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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. Zelboraf ®Summary of Product Characteristics. Last updated: 23/08/2018. Accessed Nov 2019 Available at https://www.ema.europa.eu/en/documents/product-information/zelboraf-epar-product-information_en.pdf
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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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.