

Vemurafenib (Zelboraf)

Criteria for Use

May 2013

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive vemurafenib.*

- Untreated brain metastases (See Issues for Consideration)
- Brain metastases requiring corticosteroid treatment
- Negative for the BRAF V600E mutation by the cobas® 4800 BRAF V600 Mutation Test or other FDA-approved test (see Issues for Consideration)
- Baseline QTc interval \geq 450 msec (See Issues for Consideration)
- ECOG Performance Status \geq 2
- Severe baseline hepatic impairment (Child-Pugh Class C) or severe renal impairment (creatinine clearance $<$ 30 mL/min)
- Pregnancy (Category D) [i.e., known pregnancy or positive pregnancy test]

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

- Unresectable or metastatic melanoma with a BRAF V600E mutation as detected by the FDA approved cobas® 4800 BRAF V600 Mutation Test or other FDA-approved test
- Goals of care and role of Palliative Care consult has been discussed and documented.
- Patient is followed by a VA Oncologist or locally designated VA expert in melanoma
- Pregnancy should be excluded prior to receiving vemurafenib and the patient provided contraceptive counseling on potential risk vs. benefit of taking vemurafenib if patient were to become pregnant. Women of child-bearing potential and men with partners of child-bearing potential should use appropriate contraception during therapy and for at least 2 months after discontinuation of therapy.

Dosage and Administration

Recommended starting dose is 960 mg (four 240 mg tablets) twice daily, approximately 12 hours apart without regards to meals. See the package insert for dose modifications.

Monitoring
<ul style="list-style-type: none"> • Baseline <ul style="list-style-type: none"> ○ Electrocardiogram for QTc interval ○ Electrolytes ○ Liver enzymes and bilirubin ○ Dermatologic exam; excise any cutaneous squamous cell carcinomas prior to starting therapy ○ Radiograph assessment of disease burden • During Therapy <ul style="list-style-type: none"> ○ Electrocardiogram 15 days after starting therapy, then monthly for 3 months, then every 3 months; also monitor after any dose modification ○ Liver enzymes and bilirubin monthly or as clinically indicated ○ Dermatologic exam every 2 months; excise any suspicious lesions. Continue monitoring for 6 months after stopping therapy.
Issues for Consideration
<ul style="list-style-type: none"> • Prior stereotactic therapy or surgery for brain metastases allowed if no progression of brain metastases for at least 2 months • There were small numbers of patients in the phase 2 and 3 trials (N=10 in each) with a BRAF V600K mutation. Objective response rates in these patients were slightly lower than in the entire study population. Requests for use in patients with mutations other than V600E should be adjudicated locally. Trametinib, approved for use in patients with the V600K mutation, is pending review by the VA. • Mild to moderate photosensitivity reactions have been reported. Advise patients to avoid sun exposure, wear protective clothing, and use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors. • Co-administration with drugs with narrow therapeutic windows metabolized by CYP1A2, CYP2D6, and CYP3A4 is not recommended. If co-administration is required, use caution and consider a dose reduction of the concomitant CYP1A2 and CYP2D6 drugs. • Co-administration of vemurafenib with warfarin resulted in a 18% increase in the AUC of S-warfarin. Consider additional monitoring of INR when vemurafenib is co-administered with warfarin (CYP2C9 substrate). • Vemurafenib is a substrate for CYP3A4. Co-administration with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole, etc.) or strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, etc.) may alter vemurafenib serum concentrations and should be used with caution if co-administered. • Certain conditions (e.g. paced cardiac rhythm, bundle branch block, etc.) may make interpretation of the QTc interval difficult and should be adjudicated locally.
Discontinuation Criteria
<ul style="list-style-type: none"> • Radiologic evaluation of tumor in the chest, abdomen, and pelvis should be performed periodically during therapy. Stop therapy for Progressive Disease on radiographic assessment as per RECIST version 1.1 or intolerance to therapy.

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