Official reprint from UpToDate®
www.uptodate.com ©2018 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Vemurafenib: Drug information

Copyright 1978-2018 Lexicomp, Inc. All rights reserved.

(For additional information see "Vemurafenib: Patient drug information ")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Zelboraf

Brand Names: Canada

Zelboraf

Pharmacologic Category

Antineoplastic Agent, BRAF Kinase Inhibitor

Dosing: Adult

Melanoma, metastatic or unresectable (with BRAF V600E mutation): Oral: 960 mg every 12 hours; continue until disease progression or unacceptable toxicity.

Erdheim-Chester disease (with BRAF V600 mutation): Oral: 960 mg every 12 hours; continue until disease progression or unacceptable toxicity.

Missed doses: A missed dose may be taken up to 4 hours prior to the next scheduled dose. If it is within 4 hours of the next scheduled dose, administer the next dose at the regular schedule. If vomiting occurs after a dose is taken, do not take an additional dose; continue with the next scheduled dose.

Melanoma, metastatic or unresectable (with BRAF V600K mutation) (off-label use): Oral: 960 mg every 12 hours; continue until disease progression or unacceptable toxicity (Chapman 2011; Sosman 2012).

Melanoma, metastatic or unresectable (with BRAF V600E or V600K mutations) (off-label combination): Oral: 960 mg every 12 hours (in combination with cobimetinib); continue until disease progression or unacceptable toxicity (Larkin 2014).

Non-small cell lung cancer, refractory (with BRAF V600 mutation) (off-label use): Oral: 960 mg twice daily (Hyman 2015). Additional data may be necessary to further define the role of vemurafenib in this condition.

Dosage adjustment for concomitant strong CYP3A4 inducers: Avoid concomitant use of strong CYP3A4 inducers. If concurrent use of a strong CYP3A4 inducer (eg, carbamazepine, phenytoin, rifampin) cannot be avoided, increase the vemurafenib dose by 240 mg as tolerated. After the strong CYP3A4 inducer has been discontinued for 2 weeks, resume the vemurafenib dose that was used prior to initiating the CYP3A4 inducer.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

Mild to moderate impairment (preexisting): No dosage adjustment necessary.

Severe impairment (preexisting): There are no dosage adjustments provided in the manufacturer's labeling (data are insufficient to determine if dosage adjustment is necessary); use with caution.

Nephrotoxicity/creatinine abnormalities during treatment: Refer to dosage adjustment for toxicity and manage with dose reduction, treatment interruption, or discontinuation.

Dosing: Hepatic Impairment

Mild to moderate impairment (preexisting): No dosage adjustment necessary.

Severe impairment (preexisting): There are no dosage adjustments provided in manufacturer's labeling (data are insufficient to determine if dosage adjustment is necessary); use with caution.

Hepatotoxicity/lab abnormalities during treatment: Refer to dosage adjustment for toxicity and manage with dose reduction, treatment interruption, or discontinuation.

Dosing: Adjustment for Toxicity

Note: Do not dose reduce below 480 mg twice daily. NCI Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0 used for adverse event grades.

Grade 1 or grade 2 (tolerable) toxicity: No dosage adjustment recommended.

Grade 2 (intolerable) or grade 3 toxicity:

First incident: Interrupt treatment until toxicity returns to grade 0 or 1, then resume at 720 mg twice daily

Second incident: Interrupt treatment until toxicity returns to grade 0 or 1, then resume at 480 mg twice daily

Third incident: Discontinue permanently.

Grade 4 toxicity:

First incident: Interrupt treatment until toxicity returns to grade 0 or 1, then resume at 480 mg twice daily **or** discontinue permanently

Second incident: Discontinue permanently.

Specific toxicities:

New primary cutaneous malignancies: No dosage adjustment recommended.

Severe hypersensitivity or severe dermatologic toxicity: Discontinue permanently.

QTc interval changes:

QTc >500 msec (grade ≥3): Temporarily withhold treatment, correct electrolytes and control risk factors for QT prolongation; may reinitiate with a dose reduction once QTc ≤500 msec (≤ grade 2).

QTc persistently >500 msec and >60 msec above baseline: Discontinue permanently.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Zelboraf: 240 mg

Generic Equivalent Available (US) No

Prescribing and Access Restrictions Available through specialty pharmacies. Further information may be obtained from the manufacturer, Genentech, at 1-888-249-4918, or at http://www.zelboraf.com.

Medication Guide and/or Vaccine Information Statement (VIS) An FDA-approved patient medication guide, which is available with the product information and at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202429s016lbl.pdf#page=21, must be dispensed with this medication.

Administration Doses should be administered orally in the morning and evening, ~12 hours apart. May be taken with or without a meal. If vomiting occurs after a dose is taken, do not take an additional dose; continue with the next scheduled dose.

Swallow whole with a glass of water; do not crush or chew. There are case reports of vemurafenib administration after crushing (Janson 2013; Khimani 2014), however vemurafenib is nearly insoluble in water and is manufactured as a microprecipitated bulk powder core (to improve solubility/bioavailability) within a film coated tablet (Shah 2013). Pharmacokinetics and efficacy of administration other than swallowing tablets whole have not been determined.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules. Although the manufacturer does not recommend crushing the tablets, if manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double-gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double-gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016).

Use

Melanoma, unresectable or metastatic: Treatment of unresectable or metastatic melanoma in patients with a BRAFV600E mutation (as detected by an approved test)

Limitations of use: Not indicated for treatment of wild-type BRAF melanoma

Erdheim-Chester disease: Treatment of Erdheim-Chester disease (ECD) in patients with a BRAF V600 mutation

Use: Off-Label

Melanoma, metastatic (with BRAFV600K mutation); Non-small cell lung cancer, refractory (with BRAF V600 mutation)

Medication Safety Issues

Sound-alike/look-alike issues:

Vemurafenib may be confused with axitinib, cobimetinib, dabrafenib, regorafenib, SORAfenib, trametinib, vandetanib, venetoclax, vismodegib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Cardiovascular: Prolonged Q-T interval on ECG (≤55%), hypertension (≤36%), peripheral edema (17% to 23%)

Central nervous system: Fatigue (38% to ≤55%), peripheral sensory neuropathy (≤36%), headache (23% to 27%)

Dermatologic: Maculopapular rash (9% to ≤59%), alopecia (36% to ≤55%), skin rash (37% to 52%), hyperkeratosis (24% to ≤50%; seborrheic: 10% to ≤41%; pilaris: ≤32%; actinic: 8% to ≤32%), skin photosensitivity (33% to 49%), xeroderma (16% to ≤45%), palmar-plantar erythrodysesthesia (≤41%), pruritus (23% to ≤36%), nevus (≤23%), sunburn (10% to ≤23%), papular rash (5% to ≤23%), erythema (8% to 14%)

Gastrointestinal: Diarrhea (28% to ≤50%), nausea (≤32% to 37%), vomiting (18% to 26%), decreased appetite (18% to 21%), constipation (12% to 16%), dysgeusia (11% to 14%)

Hematologic & oncologic: Cutaneous papilloma (21% to ≤55%), keratoacanthoma (≤41%), squamous cell carcinoma of skin (≤41%; grade 3: 22% to ≤36%)

Hepatic: Increased gamma-glutamyl transferase (5% to 15%)

Neuromuscular & skeletal: Arthralgia (53% to ≤82%), myalgia (13% to 24%), limb pain (9% to 18%), back pain (8% to 11%), musculoskeletal pain (8% to 11%), weakness (2% to 11%)

Renal: Increased serum creatinine (up to 3x ULN: 26% to 86%; greater than 3x ULN: 1% to 9%)

Respiratory: Cough (8% to ≤36%)

Miscellaneous: Fibrosis (Dupuytren contracture) (<20%), fever (17% to 19%)

1% to 10%:

Cardiovascular: Atrial fibrillation, hypotension, retinal vein occlusion, vasculitis

Central nervous system: Cranial nerve palsy (facial), dizziness, peripheral neuropathy

Dermatologic: Erythema nodosum, folliculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Endocrine & metabolic: Weight loss

Hematologic & oncologic: Basal cell carcinoma, malignant melanoma (new primary), squamous cell carcinoma (oropharyngeal)

Hepatic: Increased serum ALT (≥ grade 3: 3% to ≤9%), increased serum alkaline phosphatase (≥ grade 3: 3% to ≤5%), increased serum bilirubin (≥ grade 3: 2%)

Hypersensitivity: Anaphylaxis, hypersensitivity reaction

Neuromuscular & skeletal: Arthritis, panniculitis

Ophthalmic: Blurred vision, iritis, photophobia, uveitis

Frequency not defined: Hematologic & oncologic: Secondary acute myelocytic leukemia

<1%, postmarketing, and/or case reports: Acute interstitial nephritis, acute tubular necrosis, chronic myelomonocytic leukemia with NRAS mutation (progression of preexisting condition), DRESS syndrome, hepatic injury, increased serum AST, local acneiform eruptions (Ansai 2016), neutropenia, pancreatitis, plantar fasciitis, recall skin sensitization

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to vemurafenib or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Dermatologic toxicity: Dermatologic reactions have been observed, including case reports of Stevens-Johnson syndrome and toxic epidermal necrolysis. Discontinue (permanently) for severe dermatologic toxicity.

• Fibroproliferative disease: Cases of Dupuytren contracture and plantar fascial fibromatosis have been reported with vemurafenib use (Chan 2015; Perez 2017; Vandersleyen 2016). In June of 2017, the vemurafenib manufacturer issued a “Dear Healthcare Provider” letter stating that the majority of cases reported were mild to moderate, although disabling Dupuytren contracture cases have been observed. The median time to onset was 224 days from therapy initiation; the majority of patients experienced symptom resolution or improvement with interruption or discontinuation of vemurafenib (Perez 2017). Per the manufacturer, fibromatoses may require therapy interruption or treatment discontinuation.

• Hepatotoxicity: Liver injury has been reported with use, and may cause functional impairment such as coagulopathy or other organ dysfunction. Monitor transaminases, alkaline phosphatase, and bilirubin at baseline and monthly during therapy, or as clinically necessary. May require dosage reduction, therapy interruption, or discontinuation.

• Hypersensitivity: Anaphylaxis and severe hypersensitivity may occur during treatment or upon reinitiation. Serious reactions have included generalized rash, erythema, hypotension, and drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Discontinue (permanently) with severe hypersensitivity reaction.

• Malignancies: Cutaneous squamous cell carcinomas (cuSCC), keratoacanthomas, and melanoma have been reported (at a higher rate in patients receiving vemurafenib compared to control). Cutaneous SCC generally occurs early in the treatment course (median onset: 7 to 8 weeks in melanoma patients and ~12 weeks in Erdheim Chester disease [ECD] patients) and is managed

with excision (while continuing vemurafenib treatment). Approximately one-third of melanoma patients experienced >1 cuSCC occurrence and the median time between occurrences was 6 weeks. Potential risk factors for cuSCC include age ≥65 years, history of skin cancer, or chronic sun exposure. Monitor for skin lesions (with dermatology evaluation) at baseline and every 2 months during treatment; consider continued monitoring for 6 months after treatment. In patients receiving vemurafenib for the treatment of melanoma, new primary malignant melanomas have been reported (rare). Noncutaneous squamous cell carcinomas (non-cuSCC) of the head and neck have also been observed; monitor closely for signs/symptoms. Vemurafenib may promote malignancies correlated with RAS activation; monitor for signs/symptoms of other malignancies. Myeloid malignancies in patients with ECD have been reported, including patients receiving vemurafenib; monitor CBC in patients with ECD and co-existing myeloid malignancies.

• Nephrotoxicity: Acute kidney injury, including interstitial nephritis, acute tubular necrosis, and serum creatinine elevations (grades 1 to 4) have been reported. Monitor serum creatinine.

• Ocular toxicity: Uveitis (including iritis), blurred vision, and photophobia may occur; monitor for signs and symptoms. Uveitis may be managed with corticosteroid and mydriatic eye drops. Retinal vein occlusion has been reported in clinical trials.

• Pancreatitis: Pancreatitis has been reported (rare). Onset occurs within 2 weeks after initiation, with exacerbation occurring upon rechallenge at a reduced dose (Muluneh 2013). Consider evaluating unexplained abdominal pain for pancreatitis (eg, serum lipase and amylase; abdominal CT) as clinically indicated.

• Photosensitivity: Photosensitivity ranging from mild to severe has been reported. Advise patients to avoid sun exposure and wear protective clothing and use effective UVA/UVB sunscreen and lip balm (SPF ≥30) when outdoors. Dosage modifications are recommended for intolerable photosensitivity consisting of erythema ≥10% to 30% of body surface area.

• QT prolongation: QT prolongation (dose-dependent) has been observed; may lead to increased risk for ventricular arrhythmia, including torsade de pointes. Monitor electrolytes (calcium, magnesium and potassium) at baseline and with dosage adjustments. Monitor ECG at baseline, 15 days after initiation, then monthly for 3 months, then every 3 months thereafter (more frequently if clinically appropriate); also monitor with dosage adjustments. Do not initiate treatment if baseline QTc >500 msec. During treatment, if QTc >500 msec, temporarily interrupt treatment; correct electrolytes and control other risk factors for QT prolongation. May reinitiate with a dose reduction once QTc falls to <500 msec. Discontinue (permanently), if after correction of risk factors, both the QTc continues to increase >500 msec and there is >60 msec change above baseline. Do not initiate treatment in patients with electrolyte abnormalities which are not correctable, long QT syndrome, or taking concomitant medication known to prolong the QT interval.

• Radiation sensitization/recall: Radiation sensitization and recall (some cases may be severe or involve cutaneous and visceral organs) have been reported in patients treated with radiation prior to, during, or after treatment with vemurafenib; fatal cases have been reported in patients with visceral organ involvement. Monitor closely when vemurafenib is administered concomitantly or sequentially with radiation treatment.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• Elderly: May be at increased risk for adverse effects; in clinical trials, there was an increased incidence of cuSCC and keratoacanthoma, atrial fibrillation, peripheral edema, and nausea/decreased appetite in patients ≥65 years.

Other warnings/precautions:

• BRAF genomics: Only patients with a BRAF V600 mutation-positive melanoma (including BRAF V600E) will benefit from treatment; mutation must be detected and confirmed by an approved test prior to treatment. The cobas 4800 BRAF V600 Mutation Test was used in clinical trials and is FDA-approved to detect BRAF V600E mutation.

Metabolism/Transport Effects

Substrate of BCRP/ABCG2, CYP3A4 (major), P-glycoprotein/ABCB1; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** BCRP/ABCG2, CYP1A2 (moderate), CYP2D6 (weak), P-glycoprotein/ABCB1; **Induces** CYP3A4 (weak)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Afatinib: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib. Management: Per US labeling: reduce afatinib by 10mg if not tolerated. Per Canadian labeling: avoid combination if possible; if used, administer the P-gp inhibitor simultaneously with or after the dose of afatinib. *Risk D: Consider therapy modification*

Alosetron: CYP1A2 Inhibitors (Moderate) may increase the serum concentration of Alosetron. *Risk X: Avoid combination*

Amifampridine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Aminolevulinic Acid (Systemic): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid (Systemic). *Risk X: Avoid combination*

Aminolevulinic Acid (Topical): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid (Topical). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Betrixaban: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Betrixaban. Management: Decrease the betrixaban dose to an initial single dose of 80 mg followed by 40 mg once daily if combined with a P-glycoprotein inhibitor. *Risk D: Consider therapy modification*

Bilastine: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Bilastine. Management: Consider alternatives when possible; bilastine should be avoided in patients with moderate to severe renal insufficiency who are receiving p-glycoprotein inhibitors. *Risk D: Consider therapy modification*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Brentuximab Vedotin: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Brentuximab Vedotin. Specifically, concentrations of the active monomethyl auristatin E (MMAE) component may be increased. *Risk C: Monitor therapy*

Buprenorphine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk C: Monitor therapy*

Celiprolol: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Celiprolol. *Risk C: Monitor therapy*

Colchicine: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Colchicine. Colchicine distribution into certain tissues (e.g., brain) may also be increased. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a p-glycoprotein inhibitor. In those with normal renal and hepatic function, reduce colchicine dose as directed. *Risk D: Consider therapy modification*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

CYP1A2 Substrates (High risk with Inhibitors): Vemurafenib may increase the serum concentration of CYP1A2 Substrates (High risk with Inhibitors). Management: Consider alternatives to such combinations whenever possible, particularly if the CYP1A2 substrate has a relatively narrow therapeutic index. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Vemurafenib. Management: Avoid concurrent use of vemurafenib with a strong CYP3A4 inducer and replace with another agent when possible. If a strong CYP3A4 inducer is indicated and unavoidable, the dose of vemurafenib may be increased by 240 mg (1 tablet) as tolerated. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Vemurafenib. *Risk X: Avoid combination*

Dabigatran Etexilate: P-glycoprotein/ABCB1 Inhibitors may increase serum concentrations of the active metabolite(s) of Dabigatran Etexilate. Management: Dabigatran dose reductions may be needed. Specific recommendations vary considerably according to US vs Canadian labeling, specific P-gp inhibitor, renal function, and indication for dabigatran treatment. Refer to full monograph or dabigatran labeling. *Risk D: Consider therapy modification*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Digoxin: Vemurafenib may increase the serum concentration of Digoxin. Management: Avoid coadministration of vemurafenib and digoxin when possible. If concomitant use cannot be avoided, consider digoxin dose reduction. *Risk D: Consider therapy modification*

DOXOrubicin (Conventional): P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to P-glycoprotein inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

Edoxaban: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Edoxaban. Management: See full monograph for details. Reduced doses are recommended for patients receiving edoxaban for venous thromboembolism in combination with certain inhibitors. Similar dose adjustment is not recommended for edoxaban use in atrial fibrillation. *Risk D: Consider therapy modification*

Enzalutamide: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Concurrent use of enzalutamide with CYP3A4 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP3A4 substrate should be performed with caution and close monitoring. *Risk D: Consider therapy modification*

Everolimus: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Everolimus. Management: Everolimus dose reductions are required for patients being treated for subependymal giant cell astrocytoma or renal cell carcinoma. See prescribing information for specific dose adjustment and monitoring recommendations. *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

HYDROcodone: CYP3A4 Inducers (Weak) may decrease the serum concentration of HYDROcodone. *Risk C: Monitor therapy*

Hydroxychloroquine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

Indapamide: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk D: Consider therapy modification*

Ipilimumab: May enhance the hepatotoxic effect of Vemurafenib. Management: Consider alternatives to this combination when possible. Use of this combination should only be undertaken with extra close monitoring of liver function (hepatic transaminases and bilirubin) and signs/symptoms of hepatotoxicity. *Risk D: Consider therapy modification*

Macimorelin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

MiFEPRIStone: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Mitotane: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. *Risk D: Consider therapy modification*

Mizolastine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Naldemedine: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Naldemedine. *Risk C: Monitor therapy*

Naloxegol: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Naloxegol. *Risk C: Monitor therapy*

Netupitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

NiMODipine: CYP3A4 Inducers (Weak) may decrease the serum concentration of NiMODipine. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

PAZOPanib: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

Pefloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk C: Monitor therapy*

Perhexiline: CYP2D6 Inhibitors (Weak) may increase the serum concentration of Perhexiline. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Substrates: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pirfenidone: CYP1A2 Inhibitors (Moderate) may increase the serum concentration of Pirfenidone. Management: Use any such combination with caution and close monitoring for pirfenidone toxicity. Avoid the use of pirfenidone with moderate CYP1A2 inhibitors whenever CYP2C9, 2C19, 2C6, or 2E1 is also inhibited (either by the CYP1A2 inhibitor or by a third drug). *Risk D: Consider therapy modification*

Pitolisant: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Combined use of pitolisant with a CYP3A4 substrate that has a narrow therapeutic index should be avoided. Other CYP3A4 substrates should be monitored more closely when used with pitolisant. *Risk D: Consider therapy modification*

Porfimer: Photosensitizing Agents may enhance the photosensitizing effect of Porfimer. *Risk C: Monitor therapy*

Probucol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Promazine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Prucalopride: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Prucalopride. *Risk C: Monitor therapy*

QTc-Prolonging Agents (Highest Risk): May enhance the QTc-prolonging effect of other QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying): May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). Management: Avoid such combinations when possible. Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. *Risk D: Consider therapy modification*

QTc-Prolonging Agents (Moderate Risk): May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Rasagiline: CYP1A2 Inhibitors (Moderate) may increase the serum concentration of Rasagiline. *Risk D: Consider therapy modification*

RifAXIMin: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of RifAXIMin. *Risk C: Monitor therapy*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Silodosin: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. *Risk D: Consider therapy modification*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Teneligliptin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk C: Monitor therapy*

TiZANidine: CYP1A2 Inhibitors (Moderate) may increase the serum concentration of TiZANidine. Management: If combined use cannot be avoided, initiate tizanidine in adults at 2 mg and increase in 2 to 4 mg increments based on patient response. Monitor for increased effects of tizanidine, including adverse reactions. *Risk D: Consider therapy modification*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Topotecan: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Venetoclax: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Venetoclax. Management: Reduce the venetoclax dose by at least 50% in patients requiring these combinations. *Risk D: Consider therapy modification*

Verteporfin: Photosensitizing Agents may enhance the photosensitizing effect of Verteporfin. *Risk C: Monitor therapy*

VinCRIStine (Liposomal): P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of VinCRIStine (Liposomal). *Risk X: Avoid combination*

Vinflunine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk X: Avoid combination*

Warfarin: Vemurafenib may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Xipamide: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). *Risk C: Monitor therapy*

Food Interactions Grapefruit and grapefruit juice may inhibit CYP3A4-mediated metabolism of vemurafenib. Management: Avoid concurrent use.

Pregnancy Implications Adverse effects were not demonstrated in animal reproduction studies. However, based on the mechanism of action, vemurafenib may cause fetal harm if administered during pregnancy or in patients who become pregnant during treatment. Women of reproductive potential should use effective contraception methods during treatment and for at least 2 weeks after the last dose.

Breast-Feeding Considerations It is not known if vemurafenib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during treatment and for 2 weeks after the last dose.

Dietary Considerations Avoid grapefruit and grapefruit juice.

Monitoring Parameters Confirm BRAF V600 mutation status (in patients with melanoma); liver transaminases, alkaline phosphatase and bilirubin at baseline and monthly during treatment (or as clinically appropriate). Serum creatinine at baseline and periodically during treatment. Electrolytes (calcium, magnesium and potassium) at baseline and after dosage modification. ECG at baseline, 15 days after initiation, then monthly for 3 months, then every 3 months thereafter (more frequently if clinically appropriate) and with dosage adjustments. Dermatology evaluation (for new skin lesions) at baseline and every 2 months during treatment; also consider continued monitoring for 6 months after completion of treatment. Signs/symptoms of hypersensitivity reactions, uveitis, and malignancies; signs of radiation sensitization and recall. Monitor adherence.

Mechanism of Action Vemurafenib is a low molecular weight oral BRAF kinase inhibitor (potent) which inhibits tumor growth in melanomas by inhibiting kinase activity of certain mutated forms of BRAF, including BRAF with V600E mutation, thereby blocking cellular proliferation in melanoma cells with the mutation. Does not have activity against cells with wild-type BRAF. BRAF V600E activating mutations are present in ~50% of melanomas; V600E mutation involves the substitution of glutamic acid for valine at amino acid 600.

Pharmacodynamics/Kinetics

Distribution: V_d: ~106 L

Protein binding: >99%, to albumin and α_1-acid glycoprotein

Half-life, elimination: 57 hours (range: 30 to 120 hours)

Time to peak: ~3 hours

Excretion: Feces (~94%); urine (~1%)

Pricing: US

Tablets (Zelboraf Oral)

240 mg (112): $6076.45

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes

only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

Brand Names: International Zelboraf (AT, AU, BB, BE, BR, CH, CL, CR, CU, CY, CZ, DE, DK, DO, EC, EE, ES, FR, GB, GT, HK, HN, HR, HU, IE, IL, IS, JP, KR, LB, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PH, PL, PT, QA, RO, SA, SE, SG, SI, SK, SV, TH, TR, UA)

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES

1. *Alloo A, Garibyan L, LeBoeuf N, et al. Photodynamic therapy for multiple eruptive keratoacanthomas associated with vemurafenib treatment for metastatic melanoma. Arch Dermatol. 2012;148(3):363-366. [PubMed 22431777]*
2. *Ansai O, Fujikawa H, Shimomura Y, Abe R. Case of severe acneiform eruptions associated with the BRAF inhibitor vemurafenib [published online August 11, 2016]. J Dermatol. [PubMed 27511106]*
3. *Bloom KJ, Anderson SM, Schilling RC, et al, "Molecular Testing for BRAF V600 Mutations in the BRIM-2 Trial of the BRAF Inhibitor Vemurafenib in Metastatic Melanoma," J Clin Oncol, 2011, 29(15s):10523 [abstract 10523 from ASCO 2011 Annual Meeting].*
4. *Bollag G, Hirth P, Tsai J, et al, "Clinical Efficacy of a RAF Inhibitor Needs Broad Target Blockade in BRAF-Mutant Melanoma," Nature, 2010, 467(7315):596-9. [PubMed 20823850]*
5. *Callahan MK, Rampal R, Harding JJ, et al, "Progression of RAS-Mutant Leukemia During RAF Inhibitor Treatment," N Engl J Med, 2012, 367(24):2316-21. [PubMed 23134356]*
6. *Chan SW, Vorobiof DA. Dupuytren's contractures associated with the BRAF inhibitor vemurafenib: a case report. J Med Case Rep. 2015;9:158. [PubMed 26152183]*
7. *Chapman PB, Hauschild A, Robert C, et al, "Improved Survival With Vemurafenib in Melanoma With BRAF V600E Mutation," N Engl J Med, 2011, 364(26):2507-16. [PubMed 21639808]*
8. *Flaherty KT, Puzanov I, Kim KB, et al, "Inhibition of Mutated, Activated BRAF in Metastatic Melanoma," N Engl J Med, 2010, 363(9):809-19. [PubMed 20818844]*
9. *Haroche J, Cohen-Aubart F, Emile JF, et al. Reproducible and sustained efficacy of targeted therapy with vemurafenib in patients with BRAF(V600E)-mutated Erdheim-Chester disease. J Clin Oncol. 2015 ;33(5):411-418. [PubMed 25422482]*
10. *Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med. 2015;373(8):726-736. [PubMed 26287849]*
11. *Janson B, Whitney K, Wieringa S, et al. Vemurafenib – can it be crushed or chewed? Asia Pacific J Clin Oncol. 2013;0(suppl 3):146 [Abstract 299 from Clinical Oncological Society of Australia].*
12. *Khimani F, Hoban C, Williams V, et al. Efficacy of solubilized vemurafenib administered via nasogastric tube. Future Oncol. 2014;10(2):165-170. [PubMed 24490602]*
13. *Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867-1876. [PubMed 25265494]*
14. *Larkin JM, Yan Y, McArthur GA, et al. Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced BRAF-mutated melanoma. J Clin Oncol. 2015; 33(15s):9006 [Abstract 9006 from ASCO 2015 annual meeting].*
15. *McArthur GA, Ribas A, Chapman PB, et al, "Molecular Analyses From a Phase I Trial of Vemurafenib to Study Mechanism of Action (MOA) and Resistance in Repeated Biopsies From BRAF Mutation–Positive Metastatic Melanoma Patients (pts)," J Clin Oncol, 2011, 29(15s):8502 [abstract 8502 from ASCO 2011 Annual Meeting].*
16. *Muluneh B, Buie LW, and Collichio F. Vemurafenib-associated pancreatitis: case report. Pharmacotherapy. 2013;33(4):e43-e44. [PubMed 23436544]*
17. *NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40_conversion. Last accessed October 2012.*

18. *Perez EA. Dear healthcare provider letter: Risk of Dupuytren's contracture and plantar fascial fibromatosis with Zelboraf (vemurafenib). South San Francisco, CA: Genentech USA, Inc; June 2017.*

19. *Ribas A, Hodi FS, Callahan M, et al, "Hepatotoxicity With Combination of Vemurafenib and Ipilimumab," N Engl J Med, 2013, 368(14):1365-6. [PubMed 23550685]*

20. *Ribas A, Kim KB, Schuchter LM, et al, "BRIM-2: An Open-Label, Multicenter Phase II Study of Vemurafenib in Previously Treated Patients With BRAF V600E Mutation-Positive Metastatic Melanoma," J Clin Oncol, 2011, 29(15s):8509 [abstract 8509 from ASCO 2011 Annual Meeting].*

21. *Shah N, Iyer RM, Mair HJ, et al. Improved human bioavailability of vemurafenib, a practically insoluble drug, using an amorphous polymer-stabilized solid dispersion prepared by a solvent-controlled coprecipitation process. J Pharm Sci. 2013;102(3):967-981. [PubMed 23280631]*

22. *Sosman JA, Kim KB, Schuchter L, et al, "Survival in BRAF V600-Mutant Advanced Melanoma Treated With Vemurafenib," N Engl J Med, 2012, 366(8):707-14. [PubMed 22356324]*

23. *Su F, Viros A, Milagre C, et al, "RAS Mutations in Cutaneous Squamous-Cell Carcinomas in Patients Treated With BRAF Inhibitors," N Engl J Med, 2012, 366(3):207-15. [PubMed 22256804]*

24. *Su F, Yang H, Higgins B, et al, "Molecular Mechanisms Underlying Disease Relapse on Treatment With Selective BRAF Inhibitor Vemurafenib (PLX4032)," J Clin Oncol, 2011, 29(15s):8517 [abstract 8517 from ASCO 2011 Annual Meeting].*

25. *US Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2016. http://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf. Updated September 2016. Accessed October 5, 2016.*

26. *Vandersleyen V, Grosber M, Wilgenhof S, et al. Vemurafenib-associated Dupuytren- and Ledderhose palmoplantar fibromatosis in metastatic melanoma patients. J Eur Acad Dermatol Venereol. 2016;30(7):1133-1135. [PubMed 26303964]*

27. *Zelboraf (vemurafenib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; November 2017.*

28. *Zelboraf (vemurafenib) [product monograph]. Mississauga, Ontario, Canada: Hoffman-La Roche Limited; July 2017.*

Topic 16798 Version 175.0