Drug Monograph

A - Drug Name

vemURAFenib

COMMON TRADE NAME(S): Zelboraf ®

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B - Mechanism of Action and Pharmacokinetics

Vemurafenib is an orally bioavailable, small-molecule, inhibitor of BRAF kinase. Mutations of BRAF result in constitutive activation and cell proliferation. Vemurafenib selectively binds to the ATP-binding site of BRAF(V600E). There is little clinical data supporting its activity in inhibiting other mutations of BRAF.

Absorption	Bioavailability	64%
	Effects with food	Unknown
	T max	4 hours (median)
	Time to reach steady state	22 days
Distribution	Cross blood brain barrier?	No
	PPB	> 99%
Metabolism	Main enzymes involved	CYP3A4
	Inhibitor of	CYP1A2 (moderate), CYP2D6 (weak), CYP2C9, efflux transporter P-glycoprotein (as well as being a substrate)
	Inducer of	CYP3A4

Elimination	Urine	<1%
	Feces	94%
	Half-life	57 hr (range 30-120 hr)

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C - Indications and Status

Health Canada Approvals:

- Melanoma

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects were reported in ≥ 5% of patients treated with vemurafenib versus dacarbazine in a phase III study. Severe or life-threatening adverse effects from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (3%)	I E
	Cardiotoxicity (<1%)	E D
	Hypertension (3%)	E
	QT interval prolonged (2%) (> 500 ms)	E D
	Venous thromboembolism (1%)	E D
Dermatological	Alopecia (48%)	E
	Hand-foot syndrome (9%)	E
	Other (2%) (Panniculitis)	E
	Photosensitivity (41%)	E

	Radiation sensitization and recall reaction (may be severe)	I E
	Rash (41%) (may be severe)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Abdominal pain (10%)	E
	Anorexia, weight loss (22%)	E D
	Constipation (14%)	E
	Diarrhea (36%)	E
	Nausea, vomiting (38%)	I E
General	Edema (20%)	E D
	Fatigue (46%)	I E
	Fever (21%)	E
Hematological	Myelosuppression (rare)	E
Hepatobiliary	↑ LFTs (12%) (severe)	E D
	Pancreatitis (<1%)	E
Hypersensitivity	DRESS syndrome (rare)	E
	Hypersensitivity (rare)	I
Metabolic / Endocrine	↓ K (5%)	E
	Tumor lysis syndrome (rare)	E
Musculoskeletal	Musculoskeletal pain (56%)	I E
	Other (1%) Dupuytren's contracture / plantar fascial fibromatosis	E D
Neoplastic	Secondary malignancy (27%)	E D
Nervous System	Depression (5%)	D
	Dizziness (11%)	I E
	Dysgeusia (15%)	E D
	Headache (33%)	I E
	Insomnia (10%)	E
	Peripheral neuropathy (3%)	E D
Ophthalmic	Retinal vascular disorder (thrombosis, rare)	D
	Uveitis (3%) (includes iritis)	E D
Renal	Creatinine increased (40%) (severe 1%)	E
	Nephritis (interstitial; rare)	E

Respiratory	Cough, dyspnea (13%)	E
Vascular	Vasculitis (1%)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for vemurafenib include musculoskeletal pain, alopecia, fatigue, photosensitivity, rash, nausea, vomiting, diarrhea, headache, secondary malignancy, anorexia and weight loss.

The paradoxical activation of MAP kinase signaling pathways is believed to result in an increase in other malignancies. **Cutaneous Squamous Cell Carcinoma** (cuSCC, including keratoacanthoma and mixed-keratoacanthoma subtypes) has been reported in up to 27% of patients and usually occurred early in the course of treatment, with median time to the first appearance of 7 to 8 weeks. Risk factors included age (≥ 65 years), prior skin cancer, RAS mutations and chronic sun exposure. Management of cuSCC and new primary melanoma included excision without dose adjustment.

Non-cutaneous squamous cell carcinoma, other RAS mutated cancers (pancreas, CMML) and **new primary melanoma** (2%) have also been reported, as well as accelerated growth of RAS-mutated cancers, cysts and polyps.

Dupuytren's contracture and plantar fascial fibromatosis has been reported and may be severe.

Reversible **hepatic failure** has been reported with median onset 44 days after starting treatment. Vemurafenib inhibits the Bile Salt Export Pump (BSEP). The possibility of this inhibition as an underlying cause of liver injury cannot be ruled out.

Renal effects have been observed, ranging from mild/moderate creatinine increases to acute interstitial nephritis and acute tubular necrosis. Most creatinine increases appeared to be reversible;

Pancreatitis has been reported rarely, usually within two weeks of starting treatment. Unexplained abdominal pain should be investigated promptly.

Severe **hypersensitivity**, including anaphylaxis, has been reported with vemurafenib. One of the cases occurred 8 days after starting vemurafenib, with rash, fever, rigors and hypotension. Similar symptoms recurred when vemurafenib was restarted, but they resolved with drug discontinuation.

DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome has been reported with vemurafenib use. The syndrome was characterized by rash, eosinophilia, and systemic involvement (e.g. fever, lymphadenopathy, elevated transaminases and renal insufficiency). The typical time to onset was 7-25 days. Vemurafenib should be discontinued if DRESS syndrome occurs. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have also been described. Panniculitis has been reported and is more common in women.

Photosensitivity ranging from mild to severe may occur during treatment. Patients should be advised to minimize sun exposure by wearing protective clothing and using a broad spectrum UVA/UVB sun screen and lip balm (SPF ≥30) when outdoors to protect against sunburn.

QTc prolongation is common but severe in 2%. Vemurafenib is not recommended in patients with pre-existing QTc prolongation (>500 ms) and those with QTc exceeding 500 ms during treatment.

Cases of **radiation sensitization and radiation recall** have been reported in patients treated with radiation prior to, during (even when held during radiation), or following vemurafenib treatment. The most common radiation schedules used were hypofractionated. Most cases were skin reactions, but some cases involving visceral organs had fatal outcomes. Vemurafenib should not be used concurrently with radiation therapy unless the potential benefit justifies the potential risk.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Only patients with BRAF V600 mutations identified by a validated test should be treated. Data supporting effectiveness in patients with BRAF mutations other than V600E are limited.

Patients with QTc > 500 ms at baseline should not be treated.

Patients should be advised to avoid sun exposure and use sunscreen.

Adults:

Oral: 960 mg PO BID

Dosage with Toxicity:

Dose Level	Vemurafenib Dose
0	960 mg BID
-1	720 mg BID
-2	480 mg BID
-3	Discontinue

Dose modifications are not recommended for cutaneous squamous cell carcinoma.

Table A

Toxicity / Grade*	Occurrence	Recommendation
Grade 1 or Grade 2 (tolerable)	Any	No change
Grade 2 (Intolerable) or Grade 3, including photosensitivity	1st	Hold until ≤ grade 1, then restart with 1 dose level ↓
	2nd	Hold until ≤ grade 1, then restart with 1 additional dose level ↓
	3rd	Discontinue
Grade 4	1st	Discontinue permanently for skin reactions or hypersensitivity or other life-threatening organ toxicity. If other toxicity, discontinue OR hold until ≤ grade 1, then restart with 2 dose level ↓
	2nd	Discontinue
Hepatotoxicity**	Any	Consider temporary hold, dose reduction or discontinuation

Pancreatitis	Any	Hold, then consider restart with 1 dose level ↓
DRESS syndrome, Stevens-Johnson syndrome, Toxic epidermal necrolysis	Any	Discontinue permanently

* Graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)
** Defined as ALT ≥ 3 x ULN plus bilirubin ≥ 2 x ULN, or ALT ≥ 5 x ULN, or ALP ≥ 2 x ULN (without bone pathology)

Table B:

QT Prolongation:

Criteria	Occurrence	Action
QTc > 500 ms and > 60 ms increase from baseline	Any	Discontinue permanently
QTc > 500 ms during treatment and ≤ 60 ms increase from baseline	1st	Hold until QTc < 500 ms. Resume with 1 dose level ↓
	2nd	Hold until QTc < 500 ms. Resume with 1 additional dose level ↓
	3rd	Discontinue permanently

Dosage with Hepatic Impairment:

Hepatic impairment may result in higher vemurafenib exposure and related adverse effects. Refer to Table A for management of hepatic impairment during treatment.

Hepatic Impairment	Bilirubin	Starting Dose
Mild	> 1 to 1.5 x ULN	100%, caution
Moderate	> 1.5 to 3 x ULN	100%, caution
Severe	> 3 x ULN	No data

Dosage with Renal Impairment:

The appropriate dose has not been established in severe renal impairment. Refer to Table A for dose modifications with renal toxicity.

Dosage in the elderly:

Elderly patients (≥ 65 years) are at greater risk of experiencing side effects such as cuSCC, decreased appetite and cardiac effects. No adjustment to starting dose is indicated.

Dosage based on gender:

Women have an increased risk of skin and musculoskeletal toxicity. Dose modifications are not needed.

Children:

Safety and efficacy have not established in patients < 18 years of age.

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F - Administration Guidelines

- The daily doses should be given in the morning and in the evening, around 12 hours apart.
- May be administered with or without food, but administration in relation to food should be consistent.
- Film-coated tablet should be swallowed whole with a glass of water; do not crush or split.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- Avoid excessive caffeine as this may increase side effects (refer to interactions).
- If vomiting occurs after taking a dose, do not take an additional dose. Continue to take the next dose as scheduled.
- If a dose is missed, it may be given if there are more than 4 hours before the next dose. Otherwise, skip this dose and give the next one as scheduled. Never give both doses at the same time.
- Store between 15-30°C, in the original package; protect from moisture.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Vemurafenib should not be used in patients with baseline QTc > 500 ms, with wild-type BRAF tumours or where the BRAF mutation status is unknown.
- Consider benefits vs risks of starting vemurafenib in these patients:
  - Patients with uncontrolled hypertension (excluded from clinical trials)
  - Concurrent use with radiation therapy (possible severe/fatal radiation sensitization and radiation recall reaction).
- Caution in patients with increased QT interval or who are at risk (low potassium/magnesium, congenital QT prolongation, or history of arrhythmia, CHF, anti-arrhythmics, other QTc prolonging agents, prior anthracyclines), diabetes, autonomic neuropathy.
- Caution in patients with prior or concurrent cancers, especially those associated with RAS mutation.
- The concurrent use of ipilimumab and vemurafenib is not recommended since hepatotoxicity was observed in a clinical trial.
- Caution should be exercised when driving or operating a vehicle or potentially dangerous machinery due to vision problems.

Other Drug Properties:

- Carcinogenicity:
  Secondary malignancies (cutaneous squamous cell carcinoma, non-cutaneous squamous cell carcinoma, primary melanoma) are common - patients must be closely monitored and treated appropriately.

Pregnancy and Lactation:

- Teratogenicity: No
- Fetotoxicity: Yes
  Vemurafenib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment, and for **2 weeks** after the last dose.
- Fertility effects: Unknown

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H - Interactions

Vemurafenib inhibits the Bile Salt Export Pump (BSEP), but the clinical significance is unknown. The drug is an inducer of CYP3A4 and an inhibitor of CYP1A2, CYP2D6 (weak), CYP2C9, CYP2C8 (in vitro) and P-gp.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ vemurafenib concentration and/or efficacy (rifampin ↓ vemurafenib AUC by 40%)	↑ metabolism of vemurafenib	Caution; avoid strong inducers if possible
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ vemurafenib concentration and/or toxicity (itraconacole ↑ vemurafenib AUC by 40%)	↓ metabolism of vemurafenib	Caution; avoid strong inhibitors if possible. If co-administered, vemurafenib dose reduction may be required.
CYP2D6 substrates (e.g. codeine, paroxetine, metoprolol)	↑ concentration and/or toxicity of drugs primarily metabolized by CYP2D6	Vemurafenib can inhibit CYP2D6	Caution; consider dose adjustment for drugs that require CYP2D6 metabolism
CYP1A2 substrates (e.g. tizanidine, caffeine, amitriptyline, haloperidol, theophylline, duloxetine)	↑ exposure (up to 4.2 x) of drugs primarily metabolized by CYP1A2	Vemurafenib inhibits CYP1A2	Concurrent use of vemurafenib and CYP1A2 substrates with a narrow therapeutic range is not recommended. If must co-administer, monitor toxicities closely and consider reducing the dose of the CYP1A2 substrate.
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-	↓ concentration and/or efficacy of drugs requiring CYP3A4 metabolism	Vemurafenib induces CYP3A4	Caution

benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)			
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↑ substrate exposure and/or toxicity; ↑ bleeding risk with warfarin	Vemurafenib inhibits CYP2C9	Caution; monitor INR closely and adjust warfarin doses
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron) or BCRP substrates (e.g. rosuvastatin, sulfasalazine, topotecan, methotrexate, etc)	↑ concentration and/or toxicity when used with vemurafenib	Vemurafenib is a P-gp/BCRP inhibitor	Caution; dose reduction of substrate may be required
P-glycoprotein inducers (i.e. dexamethasone, rifampin) or BCRP inducers	↓ concentration and/or efficacy of vemurafenib (theoretical)	Vemurafenib is a P-gp/BCRP substrate	Caution
P-glycoprotein inhibitors (i.e. quinidine, verapamil, cyclosporine) or BCRP inhibitors (e.g. cyclosporine, gefitinib)	↑ vemurafenib concentration and/or toxicity (theoretical)	Vemurafenib is a P-gp/BCRP substrate	Caution
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine,	↑ risk of QTc prolongation and/or torsade de pointes	Synergistic	Avoid if possible; monitor closely if used together

clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)			
CYP2C8 substrates (e.g. repaglinide, paclitaxel)	Potential ↑ substrate concentration and/or toxicity	Vemurafenib moderately inhibits CYP2C8	Caution with CYP2C8 substrates with a narrow therapeutic range

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
ECG and electrolytes (including potassium, magnesium and calcium, especially in patients with risk factors for QT prolongation)	baseline and after dose modification, Day 15, monthly for first 3 months then every 3 months, or more often as clinically indicated
Liver function tests	baseline and periodic, monitor closely if abnormal
Renal function tests	baseline and periodic, monitor closely if abnormal
Blood pressure	baseline and periodic during treatment
INR in patients taking warfarin	during initiation of vemurafenib and after dose modification or discontinuation
Dermatologic evaluation	baseline and regular, until 6 months after the last dose
Head and neck examination (at least a visual inspection of oral mucosa and lymph node palpation, for NCuSCC)	baseline and every 3 months, until 6 months after the last dose

Pelvic (females) / anal examinations (for NCuSCC)	baseline, end of treatment and when clinically indicated, until 6 months after the last dose
Chest CT scan (for NCuSCC)	baseline and every 6 months, until 6 months after the last dose
Clinical toxicity assessment for musculoskeletal, skin, ocular, GI toxicity	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- vemURAFenib - Monotherapy in patients with BRAF V600 mutation-positive unresectable stage III or stage IV melanoma, with specific criteria
- vemURAFenib - In combination with cobimetinib for the treatment of patients with previously untreated BRAF V600 mutation-positive unresectable stage III or stage IV melanoma, with specific criteria

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K - References

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Chapman PB et al. Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with V600EBRAF-mutated melanoma. J Clin Oncol 2011; 29 (suppl; abstr LBA4).

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August 2023 Modified Pharmacokinetics, Adverse effects, Dosage with Toxicity, Warnings/Precautions, Pregnancy/breastfeeding and Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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