DRUG NAME: Vemurafenib

SYNONYM(S): PLX4032[1,2], RO5185426[3]

COMMON TRADE NAME(S): ZELBORAF®

CLASSIFICATION: miscellaneous (BRAF inhibitor)

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Vemurafenib is a low molecular weight inhibitor of BRAF serine-threonine kinase. It selectively suppresses cellular proliferation in tumour cells expressing mutated BRAF V600 proteins. Vemurafenib does not have activity with wild-type BRAF.[4]

PHARMACOKINETICS:

Oral Absorption	Tmax (median) is 4 hours; marked accumulation after repeat dosing; high inter-patient variability; effect of food is unknown	
Distribution	high inter-patient variability	
	cross blood brain barrier?	no
	volume of distribution	91L
	plasma protein binding	>99%
Metabolism	primarily eliminated in the liver; CYP 2C9 inhibition observed *in vitro*; 3 main metabolites (activity not characterized)	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily in feces	
	urine	<1%
	feces	94%
	terminal half life	57 h (median); high inter-patient variability
	clearance	29 L/day; high inter-patient variability
Sex	males have a greater apparent clearance and volume of distribution than females; however, relative differences in AUC and Cmax are small (no dosage adjustment required based on gender)	
Elderly	no significant difference	

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:
*Melanoma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***Secondary malignancies,*** including ***cutaneous squamous cell carcinoma*** and ***new primary melanomas,*** have been reported; dermatologic evaluations should be performed prior to treatment and regularly during treatment.[4]
- ***Non-cutaneous malignancies*** and accelerated ***progression*** of RAS-mutant cancers have been reported; use cautiously in patients with prior or concurrent cancer, particularly those associated with RAS mutations. Screening should begin prior to treatment and be repeated as indicated.[5-7]
- ***QTc prolongation*** has been observed; regular monitoring of ECG and electrolytes is recommended (refer to protocol by which patient is being treated). Risk factors for developing torsades de pointes include age (65 years or greater), history of cardiac disease or arrhythmias, electrolyte disturbances, nutritional deficits, etc. Concurrent therapy with other QT prolonging drugs may increase the risk of potentially fatal arrhythmias and should be avoided if possible.[4]
- ***Tumour Lysis Syndrome*** has been reported with vemurafenib treatment.[4]
- ***Radiation sensitization*** and ***recall reactions*** have been reported in patients treated with radiation prior to, during, and following treatment with vemurafenib.[8,9]
- ***Acute kidney injury*** has been reported; monitor serum creatinine prior to treatment and regularly thereafter.[10]

Special populations:

- Elderly patients (65 years or older) reportedly experience more adverse events, including cutaneous squamous cell carcinoma, decreased appetite, and cardiac disorders, as compared to younger patients.[4]
- Female patients reportedly experience approximately twice as many clinically significant events of arthralgia, photosensitivity reactions, and rash as compared to males.[4]

Carcinogenicity: No formal studies have been conducted; however secondary malignancies have been reported with vemurafenib.[4]

Mutagenicity: Not mutagenic in Ames test and in mammalian *in vivo* chromosome test.[4]

Fertility: No preclinical studies have been conducted; however, no findings in reproductive organs were reported in toxicology studies.[4]

Pregnancy: FDA Pregnancy Category D.[11] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Vemurafenib crosses the placenta in rats, however it was not shown to be teratogenic in rat or rabbit embryos/ fetuses. Human studies are not available. BRAF function is considered essential for the developing embryo; vemurafenib may cause fetal harm by interfering with BRAF function. Women of childbearing potential and males are recommended to use appropriate contraception during and for at least 6 months after treatment with vemurafenib.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[12,13]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	febrile neutropenia[5] (<1%)
	neutropenia[5] (<1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	atrial fibrillation (2%)
	cardiac failure (<1%)
	QTc prolongation; may require treatment interruption and dose modification; see paragraph following **Side Effects** table
eye	iritis/uveitis (3%)
	retinal vein occlusion (1%, severe 1%)[2]
gastrointestinal	*emetogenic potential:* low[14]
	abdominal pain (7-10%, severe 1-2%)
	constipation (12-17%, severe <1%)
	diarrhea (28-32%, severe <1%)
	nausea (23-42%, severe <3%)[2,4]
	pancreatitis[5,15] (<1%); see paragraph following **Side Effects** table
	vomiting (18-28%, severe 1-2%)
general disorders and administration site conditions	asthenia (2-11%, severe <1%)
	fatigue (38-57%, severe 2-4%)
	peripheral edema (17-23%, <1%)
	pyrexia (19%, severe <2%)
hepatobiliary	liver injury, including hepatic failure[5,16] (<1%); see paragraph following **Side Effects** table
immune system	hypersensitivity reactions; see paragraph following **Side Effects** table
injury, poisoning, and procedural complications	radiation sensitization and radiation recall[8,9]; see paragraph following **Side Effects** table
investigations	ALT increase (severe 3%)[2]
	AST increase (severe 1%)[2]
	alkaline phosphatase increase (severe 3%)[2]
	bilirubin increase (severe 2%)
	creatinine increase[10] (30-40%, severe 1%); see paragraph following **Side Effects** table
	gamma-glutamyltransferase increase (5-15%, severe 4-12%)[2]
	weight loss (8-10%, severe ≤1%)
metabolism and nutrition	appetite decrease (18-23%)
	dehydration (3%)
	hyperuricemia (2%)[2]
	hypokalemia (5%)
	tumour lysis syndrome (<1%)
musculoskeletal and connective tissue	***arthralgia*** (53-68%, severe 2-8%)
	arthritis (2-10%, severe <2%)
	back pain (8-11%, severe <1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	Dupuytren's contracture, plantar fascial fibromatosis[17] (1%); see paragraph following **Side Effects** table
	extremity pain (10-18%, severe <1%)
	myalgia (13-24%, severe <1%)
	musculoskeletal pain (8-12%)
neoplasms	basal cell carcinoma (3%)
	cutaneous squamous cell carcinoma (18-26%, severe 12-25%)[1,4]; see paragraph following **Side Effects** table
	melanoma, new primary (2%); see paragraph following **Side Effects** table
	seborrhoeic keratosis (10-14%, severe <1%)
	skin papilloma (21-31%, severe <1%)
	squamous cell carcinoma of head and neck (<1%)
nervous system	dizziness (8%)
	dysgeusia (11-14%)
	facial nerve paralysis (1-2%, severe 1%)[2,4]
	headache (23-29%, severe <1%)
	neuropathy, peripheral (2-11%, severe <1%)
	syncope (1%)
psychiatric	delirium (1%, severe 1%)[2]
	depression (4-10%, severe <1%)
renal and urinary	acute kidney injury (1-10%, severe <2%)[10]; see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (8-15%)
	oropharyngeal pain (4-10%)
	pulmonary embolism (≤1%)
skin and subcutaneous tissue	actinic keratosis (8-17%)
	alopecia (38-45%, severe <1%); generalized thinning on scalp, sometimes body hair[18]
	DRESS syndrome (<1%)[5,6,19]; see paragraph following **Side Effects** table
	dry skin (19%)
	erythema (10-14%)
	hyperkeratosis (24-30%, severe 1%)
	palmar-plantar erythrodysaesthesia syndrome (8-10%, severe ≤2%)[2,4]
	panniculitis, eyrthema nodosum[5,18] (2%)
	photosensitivity reaction (33-53%, severe 2-4%); see paragraph following **Side Effects** table
	pruritus (23-32%, severe 1-2%)
	rash (5-54%, severe 7-13%)
	Stevens-Johnson syndrome (<1%); see paragraph following **Side Effects** table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	sunburn (10-14%); see paragraph following **Side Effects** table
	toxic epidermal necrolysis (<1%); see paragraph following **Side Effects** table
vascular	hypertension (3%)
	vasculitis (1%)

Adapted from standard reference[4] unless specified otherwise.

The ***most common*** adverse reactions with vemurafenib include arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and cutaneous squamous-cell carcinoma.[1,2,4,20] The majority of reactions are mild to moderate in intensity. Interrupt treatment for intolerable grade 2 and higher grade toxicities. Resume treatment at a reduced dose after toxicity returns to grade 0 or 1. Dose reductions below 480 mg twice daily are not recommended.[4]

Cutaneous squamous cell carcinoma is reported with an incidence of 18-26%. The majority of the excised lesions are classified as keratoacanthoma subtype or mixed keratoacanthoma subtype. Cases occur early in treatment, with a median time to first appearance of 7-8 weeks. Potential risk factors include age (≥ 65 years), prior skin cancer, RAS gene mutations, and chronic sun exposure. Suspicious skin lesions should be excised. Treatment interruption and/or dosage adjustment is not required. Dermatologic evaluations should be conducted prior to and regularly during treatment with vemurafenib. Monitoring for cutaneous squamous cell carcinoma should continue for 6 months following discontinuation of vemurafenib.[4]

Vemurafenib treatment may increase the risk of ***non-cutaneous malignancies*** or cause the ***progression*** of cancers associated with RAS mutations due to a paradoxical activation of the MAP-kinase signalling in BRAF wild type cells exposed to BRAF inhibitors. Use with caution in patients with prior or concurrent cancer, particularly those associated with RAS mutations. Screening for other malignancies should begin prior to treatment with vemurafenib and be repeated during treatment as indicated. Suggested screening may include head and neck, pelvic, and anal examinations as well as chest CT and other tests as required. It is recommended that monitoring for non-cutaneous malignancies continue for up to 6 months after treatment discontinuation.[5,6]

New ***primary melanomas*** are reported in 2% of patients. Monitor and manage as described for cutaneous squamous cell carcinoma.[4]

Dupuytren's contracture and ***plantar fascial fibromatosis*** have been reported with vemurafenib. Although the majority of cases are mild to moderate in severity, disabling cases of Dupuytren's contracture have also been reported. Events should be managed with dose reduction, treatment interruption, or treatment discontinuation.[17]

Hepatic injury leading to functional hepatic impairment, including coagulopathy or hepatic failure can occur with vemurafenib. Elevations in transaminases, alkaline phosphatase, and bilirubin are reported. Time to onset is reportedly within 2 months of starting treatment. Manage laboratory abnormalities or suspected liver injury with dose reduction, temporary interruption, or treatment discontinuation as indicated.[5,16,21]

Hypersensitivity reactions, including anaphylaxis, have been reported. Symptoms observed include generalized rash, erythema, fever, rigors, and hypotension. Onset may sometimes be delayed (i.e., reported 8 days after treatment initiated in one case). Severe dermatologic reactions including DRESS syndrome (i.e., Drug Reaction with Eosinophilia and Systemic Symptoms), Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis have also been reported and may be life threatening.[4] Vemurafenib should be permanently discontinued in patients experiencing severe reactions.[22]

Reports of acute ***kidney injury*** range from mild to moderate creatinine elevations to acute interstitial nephritis and acute tubular necrosis. In most cases, creatinine elevations are mild to moderate (up to 3 times ULN) and reversible. The mechanism for injury appears to be tubular and interstitial damage related to BRAF inhibition. In some cases, the injury appears within 1-2 weeks of drug initiation; however, in others, the form of injury is more subacute in

nature and appears within 1-2 months. It is possible also that this kidney injury may have both an acute and chronic component. Renal function should be closely monitored for early detection of dysfunction.[10,23-26]

Cases of drug-induced ***pancreatitis*** have been reported, usually within the first two weeks after initiating treatment with vemurafenib. Prompt investigation of unexplained abdominal pain is recommended. Consider dose modification if vemurafenib is re-started following an episode of pancreatitis.[5]

Mild to severe ***photosensitivity*** has been reported, including painful blistering in some cases.[27] Onset occurs within 24 hours of sun exposure, sometimes as soon as within 15 minutes.[18] Both UVA and UVB radiation are implicated as patients may experience photosensitivity indoors from behind glass as well as following direct sun exposure.[18,28] Dose modification is suggested for intolerable grade 2 or greater events.[4] Photosensitivity is considered preventable in most patients. Minimize or avoid sun exposure, and when outdoors, use protective clothing and broad spectrum UVA/UVB sunscreen.[4,18]

QTc prolongation has been observed with vermurafenib. ECG and electrolytes should be monitored during treatment. Vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or on concurrent therapy with other QT prolonging agents. Vemurafenib should not be initiated in patients with QTc interval greater than 500 milliseconds. If grade 3 QTc prolongation (QTc greater than 500 ms) develops during treatment, vemurafenib should be held until electrolyte abnormalities are corrected and cardiac risk factors are controlled. Vemurafenib may be restarted at a reduced dose once QTc interval is below 500 ms. Vemurafenib should be permanently discontinued if QTc interval remains greater than 500 ms and is more than 60 ms above baseline.[4] Refer to protocol by which patient is being treated.

Radiation sensitization and ***recall reactions*** have been reported in targeted tissues in association with both concurrent and nonconcurrent vemurafenib. Sensitization is characterized by the potentiation of the radiation reaction, such that the severity of reaction experienced is greater than that expected for local radiation injury. The majority of sensitization reactions are reported during concurrent administration or when vemurafenib is administered within 3 days after completion of radiation. Recall reactions are evidenced by acute inflammation confined to a previously irradiated area and may be triggered by vemurafenib administration 7 days or more after completion of radiation. Most reported cases of radiation sensitization or recall are cutaneous in nature, however visceral organ involvement has also been reported, sometimes with fatal outcomes.[8,9]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dextromethorphan[4]	increased dextromethorphan AUC by an average 47%	inhibition of CYP 2D6 by vemurafenib	monitor for increased dextromethorphan toxicity
digoxin[8]	1.8 fold increase in digoxin AUC; 1.5 fold increase in digoxin Cmax	inhibition of P-glycoprotein by vemurafenib	monitor digoxin levels and adjust digoxin dose accordingly
grapefruit juice[4]	may increase plasma level of vemurafenib	may inhibit CYP 3A4 metabolism of vemurafenib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of vemurafenib treatment
midazolam[4]	decreased midazolam AUC by an average 39%	induction of CYP 3A4 by vemurafenib	monitor for decreased midazolam effect
rifampin[17]	decreased vemurafenib AUC by 40%	induction of CYP 3A4 by rifampin	avoid combination
warfarin[4,29]	increased warfarin AUC by 20% (mean)	inhibition of CYP 2C9 by vemurafenib	monitor INR and adjust warfarin dose accordingly

Drugs that have been associated with **QTc interval prolongation** and/or torsades de pointes should be avoided due to the risk of potentially fatal arrhythmias.[4]

Vemurafenib is both a substrate and an inhibitor of **P-glycoprotein (P-gp)** and **breast cancer resistance protein**. Clinical significance is unknown. Consider dose reduction of the other P-gp substrate, if applicable, when vemurafenib is given concurrently with another substrate.[8]

Vermurafenib is both a substrate and a weak/moderate inducer of **CYP 3A4**. Clinical significance is unknown.[30]

Vemurafenib is a moderate inhibitor of **CYP 1A2** and a weak inhibitor of **CYP 2D6** and **CYP 2C9**.[27,30] Consider dose modification of the substrate based on its therapeutic window.[5] Vemurafenib moderately inhibits CYP 2C8 *in vitro*.[5] Clinical significance is unknown.[5]

SUPPLY AND STORAGE:

Oral: Hoffmann-La Roche Limited supplies vemurafenib as 240 mg film-coated tablets. Store at room temperature. Keep in original packaging. Protect from moisture.[4]

Additional information: Vemurafenib is co-precipitated with hypromellose acetate succinate (HPMC-AS) to improve the aqueous solubility of vemurafenib. Vemurafenib is non-hygroscopic; however, the co-precipitate exhibits some evidence of hygroscopicity.[4]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:[1,2,4,31]	***960 mg PO twice daily*** (in the morning and in the evening, approximately 12 hours apart). Administer with food or on an empty stomach. Doses that are missed may be taken up to 4 hours prior to next scheduled dose to maintain a twice daily schedule. Do NOT take both doses at the same time.[4]
Dosage in renal failure:[11,30]	no adjustment required for pre-existing mild to moderate impairment; insufficient data in severe impairment
Dosage in hepatic failure:[4,11]	no adjustment required for pre-existing mild to moderate impairment; insufficient data in severe impairment (elimination is primarily via the liver, therefore severe liver impairment may result in higher serum levels; monitor for more frequent and/or severe exposure-related side effects, including QT prolongation)[5]
Dosage in dialysis:	no information found

Children: no information found

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