

DRUG NAME: Encorafenib

SYNONYM(S): LGX818¹

COMMON TRADE NAME(S): BRAFTOVI®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Encorafenib is an orally administered, ATP-competitive, BRAF kinase inhibitor that suppresses the MAPK pathway in tumour cells that express several mutated forms of BRAF. Mutations in the BRAF gene can result in constitutively activated BRAF kinases that stimulate tumour cell growth. Encorafenib targets BRAF V600E, V600D, and V600K, and has a longer dissociation half-life than other BRAF inhibitors, which allows for sustained target inhibition and enhanced antitumour activity. Encorafenib also targets wild-type BRAF and CRAF, and is able to bind to other kinases including JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, and STK3.¹⁻⁴

PHARMACOKINETICS:

Oral Absorption	T _{max} = 2 hours; at least 86% of dose is absorbed	
Distribution	blood to plasma concentration ratio = 0.58	
	cross blood brain barrier?	no information found
	volume of distribution	164 L
	plasma protein binding	86%
Metabolism	primarily metabolized by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	urinary and fecal elimination	
	urine	47% (2% as unchanged drug)
	feces	47% (5% as unchanged drug)
	terminal half life	3.5 h
	clearance	32 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	

Adapted from standard reference¹⁻³ unless specified otherwise.

USES:

Primary uses:

- *Melanoma
- *Colorectal cancer

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- **secondary malignancies**, including **cutaneous squamous cell carcinoma**, **new primary melanoma**, and **non-cutaneous malignancies** have been reported; begin screening for suspicious lesions prior to initiating encorafenib and monitor throughout treatment^{2,3}
- **QTc prolongation** has been observed with encorafenib; monitor ECG and electrolytes in patients with known risk factors and correct hypokalemia and/or hypomagnesemia prior to treatment^{2,3}
- **drug interactions** involving the CYP 3A4 metabolism pathway are possible and may require starting dose adjustment of encorafenib^{2,3}
- patients with pre-existing **hypertension** may experience worsening of their blood pressure control⁵

Carcinogenicity: No carcinogenicity studies have been conducted. Secondary malignancies have been reported with encorafenib.³

Mutagenicity: Not mutagenic in Ames test. Encorafenib was not clastogenic in mammalian *in vitro* or *in vivo* chromosome tests.³

Fertility: In animal studies, decreased testicular and epididymal weight, decreased tubular generation in testes, and oligospermia were observed at exposures higher than those seen following human clinical exposure.³

Pregnancy: In animal studies, decreased fetal body weights and increased incidence of total skeletal variations were observed at exposures higher than those seen following human clinical exposure. Increased post-implantation loss, including total loss of pregnancy, was observed at exposures significantly higher than those seen following human clinical exposure. Females of childbearing potential should use effective contraception during treatment and for two weeks after the last dose. Males with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose. Encorafenib may reduce the effectiveness of hormonal contraceptives via CYP 3A4 induction; alternative contraceptive measures are recommended.^{2,3}

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for two weeks after the last dose.^{2,3}

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^{5,6}.

Incidence data in the Side Effects table is based on combination therapy with another systemic treatment unless otherwise indicated with an asterisk (*). See paragraph following Side Effects table for more information on single agent encorafenib.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/ febrile neutropenia	anemia (15-37%, severe 4%)
	leukopenia (13%)
	lymphocytopenia (13-24%, severe 2-7%)
	neutropenia (13%, severe 3%)
cardiac	<i>tachycardia</i> (6%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
eye see paragraph following Side Effects table	blurred vision (4%)
	<i>retinal pigment epithelial detachment</i> (20%, severe 3%)
	<i>uveitis</i> (4%)
	<i>visual impairment</i> (20%)
gastrointestinal	<i>emetogenic potential: low</i> ⁷
	abdominal pain (28-30%, severe 4%)
	constipation (15-22%)
	<i>diarrhea</i> (33-37%, severe 2-3%)
	<i>nausea</i> (34-41%, severe <2%)
	pancreatitis (<1%)
	<i>vomiting</i> (21-30%, severe 1-2%)
general disorders and administration site conditions	<i>fatigue</i> (43-51%, severe 3-7%)
	peripheral edema (13%, severe 1%)
	pyrexia (17-18%, severe 1-4%)
immune system	hypersensitivity (1-4%)
investigations	activated partial thromboplastin time increase (12-13%, severe <5%)
	albumin decrease (16%)
	alkaline phosphatase increase (17-21%, severe <4%)
	<i>ALT increase</i> (17-29%, severe 6%)
	<i>AST increase</i> (14-27%, severe 1-3%)
	<i>creatinine increase</i> (51-93%, severe 2-4%)
	<i>gamma glutamyl transferase increase</i> (45%, severe 11-12%)
	<i>glucose increase</i> (13-28%, severe 5-6%)
	magnesium decrease (19%)
	magnesium increase (10%, severe 1%)
	potassium decrease (12-19%, severe 3%)
	<i>QTc prolongation</i> (1-3%)
	sodium decrease (10-18%, severe 2-4%)
metabolism and nutrition	appetite decrease (27%, severe 1%)
musculoskeletal and connective tissue	<i>arthralgia</i> (26-44%, severe <1%)*
	back pain (9-15%, severe <1%)*
	<i>myopathy</i> (15-33%, severe <1%)*
	pain in extremity (10-11%, severe 1%)
neoplasms	<i>basal cell carcinoma</i> (1-2%)*

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
see paragraph following Side Effects table	cutaneous squamous cell carcinoma , including keratoacanthoma (1-8%)*
	new primary melanoma (1-5%)*
nervous system	dizziness (15%, severe 3%)
	dysgeusia (6-13%)*
	facial paresis (1%)
	headache (20-22%, severe 2%)
	peripheral neuropathy (12%, severe 1%)
psychiatric	insomnia (13%)
renal and urinary	acute kidney injury (2%)
	hematuria (3%)
respiratory, thoracic and mediastinal	dyspnea (11%, severe <1%)
	epistaxis (7%)
skin and subcutaneous tissue	acneiform dermatitis (3-32%, severe <1%)*
	alopecia (14-56%)*
	dry skin (13-38%)*
	erythema (7-16%)*
	hyperkeratosis (23-57%, severe <1%)*
	melanocytic nevus (14%)
	palmar-plantar erythrodysesthesia syndrome (7-51%)*
	panniculitis (2%)
	photosensitivity (4%)
	pruritus (13-31%, severe <1%)*
	rash (22-41%, severe 1%)*
vascular	hemorrhage (19%, severe 2-3%); see paragraph following Side Effects table
	hypertension (12%, severe 6%)
	venous thromboembolism (3-6%); includes pulmonary embolism (1-3%)

Adapted from standard reference^{2,3} unless specified otherwise.

* includes incidence with single agent encorafenib (300 mg PO daily); see paragraph below

Single agent encorafenib is associated with an increased risk of certain adverse events compared to its use in combination therapy. Examples of adverse reactions observed at higher rates with single agent therapy include, but are not limited to, palmar-plantar erythrodysesthesia (51% vs 7%), hyperkeratosis (57% vs 23%), rash (41% vs 22%), alopecia (56% vs 14%), arthralgia (44% vs 26%), and grade 3 or 4 dermatologic reactions (21% vs 2%). Therefore, if the systemic treatment used in combination with encorafenib is interrupted or discontinued, encorafenib dose reduction or discontinuation is also recommended.^{2,3}

Hemorrhage and other bleeding events are reported in up to 19% of patients. The most frequently reported events are epistaxis (7%), gastrointestinal hemorrhage (4%), hematuria (3%), hematochezia (2-3%), rectal hemorrhage (2%), and hemorrhoidal hemorrhage (1%). Fatal cerebral hemorrhage has been reported in the setting of new or

progressive brain metastases. Based on the severity of the bleeding event, dose interruption, dose reduction, or treatment discontinuation may be required.^{2,3}

Based on its mechanism of action, encorafenib may promote **malignancies** associated with activation of RAS through mutation or other mechanisms. Malignancies, such as cutaneous squamous cell carcinoma (cuSCC), new primary melanoma, and non-cutaneous malignancies have been reported with encorafenib. The risk of developing second malignancies appears to be higher when encorafenib is used as a single agent versus in combination therapy. Median onset to first occurrence of cuSCC is ~6 months after encorafenib is started. Regular dermatologic evaluation is recommended throughout treatment and for up to 6 months following treatment discontinuation. Advise patients to promptly report any new skin lesions. Suspicious skin lesions should be excised. Permanently discontinue encorafenib for development of RAS mutation-positive non-cutaneous malignancies.^{2,3}

Uveitis, including iritis and iridocyclitis, and **retinal pigment epithelial detachment** have been reported. Patients reporting new or worsening visual disturbances such as diminished central vision, blurred vision, or loss of vision should be promptly referred for ophthalmological evaluation. Dose interruption, dose reduction, or treatment discontinuation may be required to manage symptoms.^{2,3}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
diltiazem ^{2,3}	2-fold increase in AUC and 45% increase in C _{max} of encorafenib	moderate inhibition of CYP 3A4 by diltiazem	avoid concurrent use; if coadministration cannot be avoided, see table below for suggested encorafenib dose reduction (monitor for encorafenib toxicity)
grapefruit juice ³	may increase plasma level of encorafenib	may inhibit CYP 3A4 metabolism of encorafenib in the intestinal wall	avoid grapefruit juice for 48 hours before and for duration of encorafenib therapy
posaconazole ^{2,3}	3-fold increase in AUC and 68% increase in C _{max} of encorafenib	strong inhibition of CYP 3A4 by posaconazole	avoid concurrent use; if coadministration cannot be avoided, see table below for suggested encorafenib dose reduction (monitor for encorafenib toxicity)

Encorafenib is a substrate of **CYP 3A4**. CYP 3A4 **inhibitors** may increase the plasma concentration of encorafenib. Avoid concurrent use with **moderate** or **strong** CYP 3A4 inhibitors if possible. If coadministration with a moderate or strong CYP 3A4 inhibitor cannot be avoided, encorafenib dose reduction is recommended (see table below). Monitor for encorafenib toxicity. Following discontinuation of the CYP 3A4 inhibitor (and after a period equaling 3-5 elimination half-lives of the inhibitor), encorafenib may be resumed at the prior dose.^{2,3}

Planned Encorafenib Dose (once daily)	Suggested Encorafenib Dose Reduction	
	Coadministered with MODERATE CYP 3A4 Inhibitor (once daily)	Coadministered with STRONG CYP 3A4 Inhibitor (once daily)
450 mg	225 mg	150 mg
300 mg	150 mg	75 mg
225 mg	75 mg	75 mg
150 mg	75 mg	75 mg

CYP 3A4 inducers may decrease the plasma concentration of encorafenib. Avoid concurrent use with **moderate** or **strong** CYP 3A4 inducers if possible.^{2,3}

Encorafenib is a reversible inhibitor of UGT1A1, CYP 1A2, CYP 2B6, CYP 2C8/9, CYP 2D6, and CYP 3A, a time-dependent inhibitor of CYP 3A4, and an inhibitor of P-gp, BCRP, OCT1, OCT2, OAT1, OAT3, OAT1B1, and OAT1B3 *in vitro*; clinical significance is unknown.^{2,3}

Encorafenib is an inducer of CYP 1A2, CYP 2B6, CYP 2C9, and CYP 3A4 *in vitro*; clinical significance is unknown.^{2,3}

Encorafenib is a substrate of P-gp; clinical significance is unknown.^{2,3}

SUPPLY AND STORAGE:

Oral: Pfizer Canada ULC supplies encorafenib as 75 mg hard gelatin capsules. Capsules contain propylene glycol. Store at room temperature. Protect from moisture.³

Additional information: Dispense encorafenib in original bottle with desiccant.³

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

Adults:

	BC Cancer usual dose noted in <i>bold, italics</i>
<i>Oral:</i> ^{2,3,8,9}	450 mg (range 225-450 mg) PO once daily
	300 mg (range 150-300 mg) PO once daily
	Administer with food or on an empty stomach. Do not take with grapefruit or grapefruit juice.
<i>Concurrent radiation:</i>	no information found
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated
<i>Dosage in renal failure:</i>	CrCl ≥ 30 mL/min: no adjustment required ^{2,3} CrCl < 30 mL/min: no information found
	calculated creatinine clearance = $\frac{N * x (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$
	* For males N=1.23; for females N=1.04
<i>Dosage in hepatic failure:</i>	mild hepatic impairment (Child-Pugh A): consider dose reduction to 300 mg PO once daily ^{2,3} moderate/severe hepatic impairment (Child-Pugh B/C): no information found
<i>Dosage in dialysis:</i>	no information found
<u>Children:</u>	safety and efficacy has not been established ³

REFERENCES:

1. Lexi-Drugs® - Lexicomp Online (database on the Internet). Encorafenib. Wolters Kluwer Clinical Drug Information Inc., 2022. Available at: online.lexi.com. Accessed January 26, 2022
2. Array BioPharma Inc. BRAVTOVI® full prescribing information. Boulder, CO, USA; April 2020
3. Pfizer Canada ULC. BRAFTOVI® product monograph. Kirkland, Quebec; March 30, 2021
4. Sullivan RJ, Weber J, Patel S, et al. A phase Ib/II study of the BRAF inhibitor encorafenib plus the MEK inhibitor binimetinib in patients with BRAF V600E/K-mutant solid tumors. *Clinical Cancer Research* 2020(26(19)):5102-12
5. Vanessa Bernstein MD. BC Cancer Melanoma Tumour Group. Personal Communication. March 30, 2022
6. Robert Tillmanns. BC Cancer Skin & Melanoma Tumour Group. Personal Communication. March 25, 2022
7. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020
8. Tabernero J, Grothey A, Cutsem EV, et al. Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study. *2021;39(4):273-284*
9. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2018(5):603-615