Drug Monograph

A - Drug Name

encorafenib

COMMON TRADE NAME(S): Braftovi®

back to top

B - Mechanism of Action and Pharmacokinetics

Encorafenib is an oral, small molecule kinase inhibitor that specifically targets BRAF V600E. BRAF mutations can result in constitutively activated BRAF kinases that may stimulate tumour cell growth. By inhibiting BRAF, encorafenib interferes with the MAPK signalling pathway that regulates the proliferation and survival of cancer cells. *In vitro*, encorafenib exhibits activity against BRAF V600 E, D, and K mutations, and targets wild-type BRAF and CRAF.

Absorption	Bioavailability	At least 86%
	Effects with food	Administration with a high-fat, high-calorie meal ↓ Cmax by 36% but no effect on AUC. Food does not appear to have clinically meaningful effects.
	T max	2 hours
	Time to reach steady state	15 days
Distribution	PPB	86%
Metabolism	Encorafenib is metabolized primarily through CYP3A4 N-dealkylation.	

Elimination	Half-life	3.5 hours
	Feces	47% (5% unchanged)
	Urine	47% (2% unchanged)

back to top

C - Indications and Status

Health Canada Approvals:

- Melanoma
- Colorectal cancer (CRC)

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

back to top

D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following adverse events were reported in ≥ 10% of patients with metastatic CRC treated with encorafenib in combination with cetuximab versus either irinotecan and cetuximab or FOLFIRI and cetuximab in a randomized Phase 3 study. It also includes severe or life-threatening adverse effects from other sources. Adverse effects reported with encorafenib in combination with binimetinib for melanoma are denoted with "^".

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	QT interval prolonged (3%)	E
	Tachycardia (6%)	E
	Venous thromboembolism (6%)	E
Dermatological	Hand-foot syndrome (4%)	E
	Other (14%) (melanocytic nevus)	E
	Photosensitivity (4%) ^	E
	Rash, pruritus (29%)	E

Gastrointestinal	Abdominal pain (30%) (4% severe)	E
	Anorexia (27%)	E
	Constipation (15%)	E
	Diarrhea (33%)	E
	Nausea, vomiting (34%)	I E
General	Fatigue (51%) (7% severe)	E
	Fever (18%) (4% severe) ^	
Hematological	Hemorrhage (19%) (2% severe)	E
Hepatobiliary	↑ LFTs (<5%) (severe)	E
	Pancreatitis (1%)	E
Hypersensitivity	Hypersensitivity (1%)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (19%) (↓ Mg, K, Na)	E
	Hyperglycemia (13%) (5% severe) ^	E
Musculoskeletal	Musculoskeletal pain (27%)	E
Neoplastic	Secondary malignancy (1%) (cutaneous or non-cutaneous)	D L
Nervous System	Headache (20%)	E
	Insomnia (13%)	E
	Other (1%) (facial paresis) ^	E
	Peripheral neuropathy (12%)	E
Ophthalmic	Retinal detachment (20%) ^	E
	Uveitis (4%) ^	E
	Visual disorders (6%)	E
Renal	Nephrotoxicity (2%)	E
Respiratory	Dyspnea (11%)	E

* "*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 encorafenib include fatigue, nausea, vomiting, abdominal pain, rash acneiform, anorexia, rash, pruritus, headache, constipation, musculoskeletal pain and skin hyperpigmentation.

When used as a **single agent**, encorafenib is associated with an increased risk of certain adverse reactions including: hand-foot syndrome, hyperkeratosis, dry skin, erythema, rash, alopecia, pruritus, arthralgia, myopathy, back pain, dysgeusia, and acneiform dermatitis. Grade 3 or 4 **dermatologic**

adverse reactions occurred in 21% of patients receiving single agent encorafenib compared to 2% of patients receiving the combination of encorafenib and binimetinib.

Based on its mechanism of action, encorafenib may promote malignancies associated with RAS activation through mutation or other pathways. **New primary malignancies**, cutaneous (e.g., cuSCC/KA) and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur with encorafenib.

Fatal cerebral **hemorrhage** has been reported in patients with new or progressive brain metastases on combination treatment with binimetinib while fatal gastrointestinal hemorrhage has been reported in patients on combination treatment with cetuximab.

Uveitis, including iritis and iridocyclitis, has been observed in patients on combination treatment with binimetinib for melanoma.

Encorafenib has been associated with serious cardiovascular adverse effects. In clinical trials, dose-dependent **QTc prolongation** occurred in 0.7% and 3.2% of patients who received encorafenib in combination with binimetinib and cetuximab, respectively. **Venous thromboembolism**, including pulmonary embolism, has also occurred while on combination treatment.

back to top

E - Dosing

Refer to protocol by which the 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.

BRAF V600 or V600E mutation should be confirmed by a validated test prior to starting encorafenib.

Correct electrolyte imbalances prior to and during treatment.

A dermatologic evaluation should be performed prior to initiating treatment.

Adults:

Various dosing and schedules are used depending on the indication. Refer to the product monograph or related regimen monographs for details.

Melanoma (in combination with binimetinib):

Oral: 450 mg Daily

Colorectal Cancer (in combination with cetuximab):

Oral: 300 mg Daily

Table 1 - Encorafenib Dose with CYP3A4 Inhibitors

Refer to Interactions Section for details on dosing modifications with CYP 3A4 inhibitors.

Planned Dose (mg daily)	Encorafenib Dose* (mg daily)	
	with Strong CYP3A4 inhibitor	with Moderate CYP3A4 inhibitor
450	150	225
300	75	150
225	75	75
150	75^	75

*Resume previous dose after the inhibitor has been discontinued for 3 to 5 half-lives.

^Monitor patients for adverse reactions and use clinical judgment; encorafenib exposure at 75mg daily (with a strong CYP3A4 inhibitor) is expected to be similar to the exposure at the 225mg daily dose (in the absence of a CYP3A4 inhibitor).

Dosage with Toxicity:

Table 2 - Dose Levels

Dose Level	Encorafenib Dose (mg daily)	
	Melanoma	Colorectal Cancer
0	450	300
-1	300	225
-2	225	150
-3	Discontinue	Discontinue

Table 3 - Dose Modifications

Also refer to the binimetinib, cetuximab and panitumumab product monographs for dose modifications of these drugs.

Toxicity / Severity		Action#
Non-cutaneous malignancy		Discontinue if RAS mutation-positive.
Any new or worsening visual disturbance		Refer to ophthalmologist.
Uveitis	Grade 1 not responding to ocular therapy	Hold encorafenib for up to 6 weeks. If improves to Grade < 1, resume at same dose.
	Grade 2 not responding to ocular therapy	Hold encorafenib for up to 6 weeks. If improves to Grade ≤ 1, resume at 1 dose level ↓.
	Grade 3	
	Grade 4	Discontinue.
QT Prolongation	QTcF > 500 ms AND ≤ 60 ms increase from baseline	Hold until QTcF ≤ 500 ms, then resume at 1 dose level ↓. If > 1 recurrence, discontinue.
	QTcF > 500 ms AND > 60 ms increase from baseline	Discontinue.
Increase in AST or ALT	Grade 2, without improvement for 2 weeks	Hold until Grade ≤ 1 or baseline. Resume at same dose.
	Grade 3 or 4	See Other Adverse Reactions below.
Hand-foot Syndrome	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1. Resume at same dose for first occurrence. Resume at same dose or with 1 dose level ↓ if recurrent.
	Grade 3	Hold until ≤ Grade 1. Resume with 1 dose level ↓.
Other Dermatologic Reactions*	Grade 2, without improvement for 2 weeks	Hold until Grade ≤ 1. Resume at same dose.

	Grade 3	Hold until Grade ≤ 1. Resume at same dose for first occurrence. Resume at 1 dose level ↓ if recurrent.
	Grade 4	Discontinue.
Other Adverse Reactions* (including hemorrhage)	Grade 2, recurrent	Hold for up to 4 weeks.
	Grade 3, 1st occurrence	If improves to Grade ≤ 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.
	Grade 3, recurrent	Consider discontinuing.
	Grade 4, 1st occurrence	Discontinue OR Hold for up to 4 weeks. If improves to Grade ≤ 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.
	Grade 4, recurrent	Discontinue.

#Encorafenib, when given in combination, may require dose reductions or discontinuation if other drugs are held or discontinued. Refer to the regimen monographs for more information.

*Excluding new primary cutaneous malignancies, other ocular events, ILD/pneumonitis, cardiac dysfunction, CPK elevation, rhabdomyolysis, and VTE.

Dosage with Hepatic Impairment:

For increased AST/ALT during treatment, refer to dose modifications table above.

Hepatic Impairment	Encorafenib Starting Dose
Mild (Child-Pugh Class A)	300 mg Daily
Moderate (Child-Pugh Class B)	No data available.
Severe (Child-Pugh Class C)	

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Encorafenib Starting Dose
≥ 30	No dose adjustment recommended
< 30	No data available.

Dosage in the elderly:

No dose adjustment required for patients ≥ 65 years. No clinically relevant differences in the safety or effectiveness were observed in patients ≥ 65 years compared to younger patients on combination treatment with binimetinib. There is insufficient data with the use of encorafenib and cetuximab in patients ≥ 65 years or older to assess differences in efficacy or safety compared to younger patients.

Dosage based on gender:

Sex does not have a clinically meaningful effect on the pharmacokinetics of encorafenib.

Children:

The safety and effectiveness of encorafenib in children < 18 years have not been established.

back to top

F - Administration Guidelines

- Administer encorafenib with or without food.
- Capsules should be swallowed whole with water. Do not crush, dissolve, or open capsules.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during encorafenib treatment.
- If a dose is missed, patient may take within 12 hours of the missed dose. If more than 12 hours has elapsed from the missed dose, the dose should be skipped and taken at the next scheduled time. Extra capsules should not be taken to make up for a missed dose.
- Do not take an additional dose if vomiting occurs after taking encorafenib.
- Store at 15 - 30°C in the original bottle. Protect from moisture and do not remove the desiccant.

back to top

G - Special Precautions

Contraindications:

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

Other Warnings/Precautions:

- Patients must have a validated test to confirm BRAF V600/E mutation before treatment; paradoxical activation of MAP-kinase signaling may occur when BRAF wild-type cells are exposed to BRAF inhibitors, such as encorafenib.
- Exercise caution in patients with diabetes or with risk factors for QT prolongation, including known long QT syndromes, bradyarrhythmias, heart failure, and taking other QT prolonging agents.
- Patients were excluded from clinical trials if they have a history of Gilbert's syndrome, abnormal LVEF, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. Consider benefits vs risks of using encorafenib in these patients.
- Use caution when driving or operating a vehicle or potentially dangerous machinery as vision problems have been reported.

Other Drug Properties:

- Carcinogenicity:
  New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur with encorafenib.

Pregnancy and Lactation:

- Genotoxicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Encorafenib is not recommended for use in pregnancy. Adequate non-hormonal contraception should be used by patients and their partners during treatment, and for at least **2 weeks** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **2 weeks** after the last dose
- Fertility effects: Probable
  No fertility data in humans. Adverse effects on male reproductive organs have been seen in animals.

back to top

H - Interactions

Encorafenib is metabolized mainly by CYP3A4, with lesser contribution from CYP2C19 and CYP2D6, and is a substrate of P-gp *in vitro*.

In vitro, encorafenib is a reversible inhibitor of UGT1A1, CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, and CYP3A, a time-dependent inhibitor of CYP3A4, and an inhibitor of P-gp, OCT1, OCT2, and OAT1, and OAT3.

Encorafenib is a strong inducer of CYP3A4 at steady-state, and also induced CYP1A2, CYP2B6, and CYP2C9 *in vitro*.

Coadministration with sensitive CYP2C19, CYP2B6, or CYP2C9 substrates may result in increased toxicity or decreased efficacy of these agents.

Coadministration of encorafenib (UGT1A1 inhibitor) with binimetinib (UGT1A1 substrate) had no effect on binimetinib exposure. Coadministration of encorafenib with cetuximab had no clinically relevant effect on pharmacokinetics.

Coadministration of a proton pump inhibitor (i.e., rabeprazole) had no effect on encorafenib exposure.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inhibitors (e.g., itraconazole, posaconazole, clarithromycin, ritonavir)	↑ encorafenib exposure (↑ AUC 3-fold and ↑ Cmax by 68% with posaconazole)	↓ metabolism of encorafenib	Avoid if possible. Reduce encorafenib dose if used in combination. See Table 1 in Dosing section.
Moderate CYP3A4 (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ encorafenib exposure (↑ AUC 2-fold and ↑ Cmax by 45% with diltiazem)	↓ metabolism of encorafenib	Avoid if possible. Reduce encorafenib dose if used in combination. See Table 1 in Dosing section.
Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin,	↓ encorafenib exposure	↑ metabolism of encorafenib	Avoid concomitant use.

rifabutin, rifampin, St. John's Wort)			
Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil)	↓ encorafenib exposure	↑ metabolism of encorafenib	Avoid concomitant use. If unavoidable, no change in encorafenib dose when used in combination.
CYP3A4 substrates (e.g., hormonal contraceptives, atorvastatin, midazolam)	↓ AUC and Cmax of substrate	Encorafenib is an inducer of CYP3A4.	Avoid concomitant use with substrates where a minimal decrease in concentration may lead to therapeutic failure. If coadministration of a sensitive substrate cannot be avoided, adjust substrate dose based on its product monograph recommendations.
CYP1A2 substrates (e.g., caffeine)	↑ risk of toxicity	Encorafenib is a reversible inhibitor of CYP1A2.	Caution, monitor for substrate toxicity.
Drugs that prolong QT Interval (e.g., amiodarone, furosemide)	↑ risk of toxicity	Additive	Avoid concomitant use with QT/QTc prolonging agent.
OATP1B1, OATP1B3 or BCRP substrates (e.g., rosuvastatin)	↑ substrate exposure (↑ AUC 1.6-fold and ↑ Cmax 2.7-fold of rosuvastatin)	Encorafenib is an inhibitor of OATP1B1, OATP1B3 and/or BCRP.	Caution, monitor for substrate toxicity. Consider dose adjustment of substrate.

back to top

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
Liver function tests	Baseline, monthly, and as clinically indicated
Renal function tests and electrolytes, including potassium and magnesium	Baseline, monthly, and as clinically indicated
CBC	Baseline, and as clinically indicated
Skin examination for any new cutaneous malignancies	Baseline, every 2 months during treatment, and continue for up to 6 months after the last dose
ECG (especially in patients at risk for QT prolongation)	Baseline and as clinically indicated
Clinical toxicity assessment for bleeding, thromboembolism, hypersensitivity, fatigue, hyperglycemia, new primary non-cutaneous malignancies, rash, ocular, and GI effects	At each visit

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

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- encorafenib - In combination with cetuximab or panitumumab in previously treated BRAF V600E-mutated metastatic colorectal cancer, according to clinical criteria
- encorafenib - For the treatment of patients with locally advanced unresectable or metastatic melanoma with a BRAF V600 mutation, according to clinical criteria.

back to top

K - References

Heinzerling L, Eigentler TK, Fluck M, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO Open. 2019 May 23;4(3):e000491.

Hesketh, P. et al. Antiemetics: ASCO Guideline Update. Journal of Clinical Oncology 2020 38:24, 2782-2797.

Kopetz, S. et al. Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E–Mutated Colorectal Cancer. N Engl J Med 2019.

Product Monograph: Braftovi® (encorafenib). Pfizer Canada ULC. February 23, 2024.

Proietti I. et al. BRAF Inhibitors: Molecular Targeting and Immunomodulatory Actions. Cancers (Basel). 2020 Jul 7;12(7):1823.

Summary of Product Characteristics: Braftovi. Pierre Fabre Limited. September 14, 2022.

April 2024 Modified Interactions section

back to top

L - Disclaimer

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top