Encoraf

Encorafenib INN

Everest

COMPOSITION

ENCORAF capsule: Each capsule contains Encorafenib INN 75 mg.

PHARMACOLOGY

Encorafenib is a selective kinase inhibitor targeting BRAF V600E, wild-type BRAF, and CRAF. It inhibits tumor cell growth in BRAF V600-mutant models and demonstrates anti-tumor activity through RAF/MEK/ERK pathway suppression. Encorafenib also binds other kinases (e.g., JNK, MEK4) at clinically relevant concentrations.
When used in combination with Binimetinib (a MEK inhibitor), Encorafenib enhances anti-tumor effects and delays resistance. In BRAF V600E-mutant colorectal cancer, Encorafenib combined with Cetuximab shows improved efficacy by overcoming EGFR-mediated resistance.

INDICATION

Encorafenib is indicated for the treatment of patients with:
• Unresectable or metastatic melanoma in combination with Binimetinib with a BRAF V600E or V600K mutation
• Metastatic colorectal cancer (mCRC) with a BRAF V600E mutation in combination with Cetuximab and mfolfox6
• Metastatic CRC with a BRAF V600E mutation in combination with Cetuximab
• Metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation in combination with Binimetinib.

Limitations of Use

Encorafenib is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF CRC, or wild-type BRAF NSCLC

DOSAGE AND ADMINISTRATION

Melanoma: The recommended dose is 450 mg orally once daily in combination with Binimetinib.
CRC: The recommended dose is 300 mg orally once daily in combination with Cetuximab.
NSCLC: The recommended dose is 450 mg orally once daily in combination with Binimetinib.

Take Encorafenib with or without food.

Dose Modification

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma or BRAF V600E Mutation-Positive Metastatic NSCLC
If Binimetinib is withheld, reduce Encorafenib to a maximum dose of 300 mg (four 75 mg capsules) once daily until Binimetinib is resumed.
Dose reductions for adverse reactions associated with Encorafenib are presented in Table 1.

Table 1: Recommended Dose Reductions for Encorafenib for Adverse Reactions – Melanoma or NSCLC

Action	Recommended Dose
First Dose Reduction	300 mg (four 75 mg capsules) orally once daily
Second Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate Encorafenib 225 mg (three 75 mg capsules) once daily

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)
If Cetuximab is discontinued, discontinue Encorafenib.
Dose reductions for adverse reactions associated with Encorafenib are presented in Table 2.

Table 2: Recommended Dose Reductions for Encorafenib for Adverse Reactions – CRC

Action	Recommended Dose
First Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Second Dose Reduction	150 mg (two 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate Encorafenib 150 mg (two 75 mg capsules) once daily

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma, BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC), or BRAF V600E Mutation-Positive NSCLC
Dosage modifications for adverse reactions associated with Encorafenib are presented in Table 3.

Table 3: Recommended Dosage Modifications for Encorafenibfor Adverse Reactions

Severity of Adverse Reaction	Dose Modification for Encorafenib
New Primary Malignancies	
Noncutaneous RAS Mutation-positive Malignancies	Permanently discontinue Encorafenib.
Cardiomyopathy	
Symptomatic congestive heart failure or absolute decrease in LVEF of greater than 20% from baseline that is also below LLN	Reduce Encorafenib by one dose level • If LVEF improves to at least institutional LLN and absolute decrease to less than or equal to 10% compared to baseline, continue Encorafenib at the reduced dose. • If no improvement, withhold Encorafenib until improves to at least institutional LLN and absolute decrease to less than or equal to 10% compared to baseline and then resume at the reduced dose or reduce dose an additional dose level.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain Encorafenib dose. • If no improvement within 4 weeks, withhold Encorafenib until improves to Grade 0-1 or to pretreatment/baseline levels and then resume at same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions.
Uveitis	
Grade 1–3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold Encorafenib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue Encorafenib.
Grade 4	Permanently discontinue Encorafenib.
QTc Prolongation	
QTcF greater than 500 ms and less than or equal to 60 ms increase from baseline	Withhold Encorafenib until QTcF less than or equal to 500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue Encorafenib.
QTcF greater than 500 ms and greater than 60 ms increase from baseline	Permanently discontinue Encorafenib.
Dermatologic [other than Hand-foot Skin Reaction (HFSR)]	
Grade 2	If no improvement within 2 weeks, withhold Encorafenib until Grade 0–1. Resume at same dose.
Grade 3	Withhold Encorafenib until Grade 0–1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 4	Permanently discontinue Encorafenib.
Other Adverse Reactions (including Hemorrhage) and HFSR	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold Encorafenib for up to 4 weeks. • If improves to Grade 0–1 or to pretreatment/baseline level, resume at reduced dose. • If no improvement, permanently discontinue Encorafenib.
First occurrence of any Grade 4	Permanently discontinue Encorafenib or Withhold Encorafenib for up to 4 weeks. • If improves to Grade 0–1 or to pretreatment/baseline level, then resume at reduced dose. • If no improvement, permanently discontinue Encorafenib.
Recurrent Grade 3	Consider permanently discontinuing Encorafenib.
Recurrent Grade 4	Permanently discontinue Encorafenib.

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Dose modification of Encorafenib when administered with Binimetinib or with Cetuximab is not recommended for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.

Refer to the Binimetinib or Cetuximab prescribing information for dose modifications for adverse reactions associated with each product, as appropriate.

Dose Modifications for Coadministration with Strong or Moderate CYP3A4 Inhibitors

Avoid coadministration of Encorafenib with strong or moderate CYP3A4 inhibitors. If coadministration is unavoidable, reduce the Encorafenib dose according to the recommendations in Table 4. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor.

Table 4: Recommended Dose Reductions for Encorafenib for Coadministration with Strong or Moderate CYP3A4 Inhibitors

Current Daily Dose*	Dose for Coadministration with Moderate CYP3A4 Inhibitor	Dose for Coadministration with Strong CYP3A4 Inhibitor
450 mg	225 mg (three 75 mg capsules)	150 mg (two 75 mg capsules)
300 mg	150 mg (two 75 mg capsules)	75 mg
225 mg	75 mg	75 mg
150 mg	75 mg	75 mg†

*Current daily dose refers to recommended dose of Encorafenib based on indication or reductions for adverse reactions based on dosing recommendations in Table 1 (Melanoma) and Table 2 (CRC).
†Encorafenib exposure at the 75 mg QD Encorafenib dosage when coadministered with a strong CYP3A4 inhibitor is expected to be higher than at the 150 mg QD dosage in the absence of a CYP3A4 inhibitor and similar to exposure at the 225 mg QD dosage in the absence of a CYP3A4 inhibitor. Monitor patients closely for adverse reactions and use clinical judgement when using Encorafenib with strong CYP3A4 inhibitors at the 150 mg dose level.

CONTRAINDICATION

None.

ADVERSE REACTION

The following adverse reactions are described elsewhere in the labeling:
• New Primary Malignancies.
• Tumor Promotion in BRAF Wild-Type Tumors
• Cardiomyopathy
• Hepatotoxicity
• Hemorrhage
• Uveitis
• QT Prolongation
• Embryo-Fetal Toxicity
• Risks Associated with Encorafenib as a Single Agent
• Risks Associated with Combination Treatment

WARNINGS AND PRECAUTION

New Primary Malignancies

New primary malignancies, cutaneous and noncutaneous, have been observed in patients treated with BRAF inhibitors and can occur with Encorafenib.

Cutaneous Malignancies

In COLUMBUS, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6%, and basal cell carcinoma occurred in 1.6% of patients who received Encorafenib in combination with Binimetinib. Median time to first occurrence of cuSCC/KA was 5.8 months (range 1 to 9 months).For patients who received Encorafenib as a single agent, cuSCC/KA was reported in 8%, basal cell carcinoma in 1%, and a new primary melanoma in 5% of patients.In BEACON CRC, cuSCC/KA occurred in 1.4% of patients with CRC, and a new primary melanoma occurred in 1.4% of patients who received Encorafenib in combination with Cetuximab. In PHAROS, cuSCC and skin papilloma, each occurred in 2% of patients who received Encorafenib in combination with Binimetinib.

In BREAKWATER, skin papilloma was reported in 2.6%, basal cell carcinoma in 1.3%, squamous cell carcinoma of skin in 0.9%, keratoacanthoma in 0.4% and malignant melanoma in situ in 0.4% of patients who received Encorafenib in combination with Cetuximab and mFOLFOX6.
Perform dermatologic evaluations prior to initiating treatment, every 2 months during treatment, and for up to 6 months following discontinuation of treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Dose modification is not recommended for new primary cutaneous malignancies.

Noncutaneous Malignancies

Based on its mechanism of action, Encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Monitor patients receiving Encorafenib for signs and symptoms of noncutaneous malignancies. Discontinue Encorafenib for RAS mutation-positive noncutaneous malignancies.

Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation prior to initiating Encorafenib.

Cardiomyopathy

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients treated with Encorafenib in combination with Binimetinib. In COLUMBUS, evidence of cardiomyopathy (decreased in LVEF below the institutional LLN with an absolute decreased in LVEF ≥10% below baseline as detected by echocardiography or MUGA) occurred in 7% of patients

receiving Encorafenib plus Binimetinib. Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) in patients receiving Encorafenib in combination with Binimetinib was 3.6 months (range 0 to 21 months). Cardiomyopathy resolved in 87% of patients receiving Encorafenib plus Binimetinib.

In PHAROS, evidence of cardiomyopathy (decrease in LVEF below the institutional LLN with an absolute decrease in LVEF ≥10% below baseline as detected by echocardiography or MUGA) occurred in 11% of patients receiving Encorafenib in combination with Binimetinib. Grade 3 left ventricular dysfunction occurred in 1% of patients. Cardiomyopathy resolved in 82% of patients receiving Encorafenib plus Binimetinib.

Assess ejection fraction by echocardiogram or MUGA scan prior to initiating treatment, one month after initiating treatment, and every 2 to 3 months during treatment. The safety of Encorafenib in combination with Binimetinib has not been established in patients with baseline ejection fraction that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely when treated with Encorafenib. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity

Hepatotoxicity can occur when Encorafenib is administered in combination with Binimetinib. In COLUMBUS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving Encorafenibin combination with Binimetinib was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. In PHAROS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving Encorafenib in combination with Binimetinib was 10% for AST, 9% for ALT, and 3.2% for alkaline phosphatase.

In BREAKWATER, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving Encorafenibin combination with Cetuximab and mFOLFOX6 was 2.2% for alkaline phosphatase, 1.3% for ALT, and 0.9% for AST.
Monitor liver laboratory tests before initiation of Encorafenib, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage

In COLUMBUS, hemorrhage occurred in 19% of patients receiving Encorafenib in combination with Binimetinib; Grade 3 or greater hemorrhage occurred in 3.2% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients.
In BEACON CRC, hemorrhage occurred in 19% of patients receiving Encorafenib in combination with Cetuximab; Grade 3 or higher hemorrhage occurred in 1.9% of patients, including fatal gastrointestinal hemorrhage in 0.5% of patients. The most frequent hemorrhagic events were epistaxis (6.9%), hematochezia (2.3%), and rectal hemorrhage (2.3%).

In PHAROS, hemorrhage occurred in 12% of patients receiving Encorafenib in combination with Binimetinib including fatal hemorrhage intracranial (1%); Grade 3 or 4 hemorrhage occurred in 4.1% of patients. The most frequent hemorrhagic events were anal hemorrhage and hemothorax (2% each).
In BREAKWATER, hemorrhage occurred in 30% of patients receiving Encorafenib in combination with Cetuximab and mFOLFOX6; Grade 3 or 4 hemorrhage occurred in 3% of patients.
Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with Encorafenib in combination with Binimetinib. In COLUMBUS, the incidence of uveitis among patients treated with Encorafenib in combination with Binimetinib was 4%. In PHAROS, the incidence of uveitis among patients treated with Encorafenibin combination with Binimetinib was 1%.
Assess for visual symptoms at each visit. Perform an ophthalmologic evaluation at regular intervals and for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

QT Prolongation

Encorafenib is associated with dose-dependent QTc interval prolongation in some patients. In COLUMBUS, an increase in QTcF to >500 ms was measured in 0.5% (1/192) of patients who received Encorafenibin combination with Binimetinib. In PHAROS, an increase in QTcF to >500 ms was measured in 2.1% (2/95) of patients who received Encorafenib in combination with Binimetinib. In BREAKWATER, an increase of QTcF >500 ms was measured in 3.6% (8/222) of patients receiving Encorafenib in combination with Cetuximab and mFOLFOX6.

Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during Encorafenib administration. Withhold, reduce dose, or permanently discontinue for QTc >500 ms.

Embryo-Fetal Toxicity

Based on its mechanism of action, Encorafenib can cause fetal harm when administered to a pregnant woman. Encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the recommended dose of 450 mg, with no clear findings at lower doses.
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use an effective, nonhormonal method of contraception since Encorafenib can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the last dose of Encorafenib.

Risks Associated with Encorafenib as a Single Agent

Encorafenib when used as a single agent is associated with an increased risk of certain adverse reactions compared to when Encorafenib is used in combination with Binimetinib. In COLUMBUS, Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with Encorafenib single agent compared to 2% of patients treated with Encorafenib in combination with Binimetinib.
If Binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of Encorafenib as recommended.

Risks Associated with Combination Treatment

Encorafenib is indicated for use as part of a regimen in combination with Binimetinib, in combination with Cetuximab, or in combination with Cetuximab and mFOLFOX6. Refer to the prescribing information for Binimetinib, Cetuximab and individual product components of mFOLFOX6 for additional risk information.

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on its mechanism of action, Encorafenib can cause fetal harm when administered to a pregnant woman. There are no available clinical data on the use of Encorafenib during pregnancy. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Lactation

There are no data on the presence of Encorafenib or its metabolites in human milk or the effects of Encorafenib on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from Encorafenib, advise women not to breastfeed during treatment with Encorafenib and for 2 weeks after the last dose.

Females and Males of Reproductive Potential

Encorafenib can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Encorafenib.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Encorafenib and for 2 weeks after the last dose. Counsel patients to use a nonhormonal method of contraception since Encorafenib has the potential to render hormonal contraceptives ineffective.

Infertility

Males

Based on findings in male rats at doses approximately 13 times the human exposure at the 450 mg clinical dose, use of Encorafenib may impact fertility in males.

Pediatric Use

The safety and efficacy of Encorafenib in pediatric patients younger have not been established.

Hepatic Impairment

No Encorafenib dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Class A). A recommended dosage has not been established in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Renal Impairment

No Encorafenib dosage adjustment is recommended in patients with mild to moderate renal impairment (CLcr 30 to <90 mL/min). A recommended dosage has not been established in patients with severe renal impairment (CLcr <30 mL/min).

OVERDOSE

Since Encorafenib is 86% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with Encorafenib.

DRUG INTERACTIONS

Effect of Other Drugs on Encorafenib

Strong or Moderate CYP3A4 Inhibitors: Coadministration of Encorafenib with a strong or moderate CYP3A4 inhibitor increases Encorafenib plasma concentrations and may increase Encorafenib adverse reactions. Avoid coadministration of Encorafenib with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the Encorafenib dose.

Strong CYP3A4 Inducers: Coadministration of Encorafenib with a strong CYP3A4 inducer may decrease Encorafenib plasma concentrations and may decrease Encorafenib efficacy. Avoid coadministration of Encorafenib with strong CYP3A4 inducers.

Effect of Encorafenib on Other Drugs

Sensitive CYP3A4 Substrates: Encorafenib is a strong CYP3A4 inducer at steady-state. Concomitant use of Encorafenib may decrease the plasma concentrations of CYP3A4 substrates (including hormonal contraceptives), which may reduce the efficacy of these substrates. Avoid the coadministration of Encorafenib with CYP3A4 substrates for which a decrease in plasma concentration may lead to reduced efficacy of the substrate. If the coadministration cannot be avoided, see the CYP3A4 substrate product labeling for recommendations.

OATP1B1, OATP1B3, or BCRP Substrates

Coadministration of Encorafenib with OATP1B1, OATP1B3, or BCRP substrates can result in increased concentrations of the substrates, and may increase toxicity of these agents. When used in combination, monitor patients closely for signs and symptoms of increased exposure and consider adjusting the dose of these substrates.

Drugs That Prolong the QT Interval

Encorafenib is associated with dose-dependent QTc interval prolongation. Avoid coadministration of Encorafenib with drugs known to prolong the QT/QTc interval.

PHARMACEUTICAL INFORMATION

Storage

Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied

ENCORAF capsule: Each HDPE container contains 90 capsules (each capsule contains Encorefenib INN 75 mg), a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com
1901000239