HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRAFTOVI safely and effectively. See full prescribing information for BRAFTOVI.

BRAFTOVI™ (encorafenib) capsules, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
BRAFTOVI is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. (1, 2.1)

Limitations of Use:
BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma. (1, 5.2)

----------DOSAGE AND ADMINISTRATION----------
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to the initiation of BRAFTOVI. (2.1)
- The recommended dose is 450 mg orally once daily in combination with binimetinib. Take BRAFTOVI with or without food. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 50 mg and 75 mg. (3)

----------CONTRAINDICATIONS----------
- None. (4)

----------WARNINGS AND PRECAUTIONS----------
- New Primary Malignancies, cutaneous and non-cutaneous: Can occur. Monitor for malignancies and perform dermatologic evaluations prior to, while on therapy, and following discontinuation of treatment. (5.1)
- Tumor Promotion in BRAF Wild-Type Tumors: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Hemorrhage: Major hemorrhagic events can occur. (5.3)
- Uveitis: Perform ophthalmologic evaluation at regular intervals and for any visual disturbances. (5.4)
- QT Prolongation: Monitor electrolytes before and during treatment. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation. Withhold BRAFTOVI for QTc of 500 ms or greater. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females with reproductive potential of potential risk to the fetus and to use effective non-hormonal method of contraception. (5.6, 8.1, 8.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥25%) for BRAFTOVI, in combination with binimetinib, are fatigue, nausea, vomiting, abdominal pain, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Array BioPharma at 1-844-792-7729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong or moderate CYP3A4 inhibitors: Concomitant use may increase encorafenib plasma concentration. If concomitant use cannot be avoided, modify BRAFTOVI dose. (2.4, 7.1)
- Strong or moderate CYP3A4 inducers: Concomitant use may decrease encorafenib plasma concentrations. Avoid concomitant use. (7.1)
- Sensitive CYP3A4 substrates: Concomitant use with BRAFTOVI may increase toxicity or decrease efficacy of these agents. Avoid hormonal contraceptives. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)
- Males of Reproductive Potential: BRAFTOVI may impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BRAFTOVI™ is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (14)]*. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage of BRAFTOVI is 450 mg orally taken once daily in combination with binimetinib until disease progression or unacceptable toxicity. Refer to the binimetinib prescribing information for recommended binimetinib dosing information.

BRAFTOVI may be taken with or without food *[see Clinical Pharmacology (12.3)]*. Do not take a missed dose of BRAFTOVI within 12 hours of the next dose of BRAFTOVI.

Do not take an additional dose if vomiting occurs after BRAFTOVI administration but continue with the next scheduled dose.

2.3 Dosage Modifications for Adverse Reactions

If binimetinib is withheld, reduce BRAFTOVI to a maximum dose of 300 mg once daily until binimetinib is resumed *[see Warnings and Precautions (5.7)]*.

Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 1.

Table 1: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions

Action	Recommended Dose
First Dose Reduction	300 mg orally once daily
Second Dose Reduction	200 mg orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 200 mg once daily

Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 2.

Table 2: Recommended Dosage Modifications for BRAFTOVI for Adverse Reactions

Severity of Adverse Reaction[a]	Dose Modification for BRAFTOVI
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Non-Cutaneous RAS Mutation-positive Malignancies	Permanently discontinue BRAFTOVI.
Uveitis [see Warnings and Precautions (5.4)]	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold BRAFTOVI for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue BRAFTOVI.
• Grade 4	Permanently discontinue BRAFTOVI.
QTc Prolongation [see Warnings and Precautions (5.5)]	
• QTcF greater than 500 ms and less than or equal to 60 ms increase from baseline	Withhold BRAFTOVI until QTcF less than or equal to 500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue BRAFTOVI.
• QTcF greater than 500 ms and greater than 60 ms increase from baseline	Permanently discontinue BRAFTOVI.
Hepatotoxicity	
• Grade 2 AST or ALT increased	Maintain BRAFTOVI dose. • If no improvement within 4 weeks, withhold BRAFTOVI 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*.
Dermatologic	
• Grade 2	If no improvement within 2 weeks, withhold BRAFTOVI until Grade 0-1. Resume at same dose.
• Grade 3	Withhold BRAFTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue BRAFTOVI.
Other Adverse Reactions (including Hemorrhage [see Warnings and Precautions (5.3)])[b]	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold BRAFTOVI 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 BRAFTOVI.
• First occurrence of any Grade 4	Permanently discontinue BRAFTOVI or Withhold BRAFTOVI 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 BRAFTOVI.
• Recurrent Grade 3	Consider permanently discontinuing BRAFTOVI.
• Recurrent Grade 4	Permanently discontinue BRAFTOVI.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[b] Dose modification of BRAFTOVI when administered with binimetinib is not recommended for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; cardiac dysfunction; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.

Refer to the binimetinib prescribing information for dose modifications for adverse reactions associated with binimetinib.

2.4 Dose Modifications for Coadministration of Strong or Moderate CYP3A4 Inhibitors

Avoid concurrent use of strong or moderate CYP3A4 inhibitors during treatment with BRAFTOVI. If concomitant use of a strong or moderate CYP3A4 inhibitor is unavoidable, reduce the BRAFTOVI dose to one-third of the BRAFTOVI dose prior to concurrent use of strong CYP3A4 inhibitors or one-half of the BRAFTOVI dose prior to concurrent use of moderate CYP3A4 inhibitors. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the BRAFTOVI dose that was taken prior to initiating the CYP3A4 inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules, hard gelatin:

- 50 mg: stylized "A" on orange cap and "LGX 50mg" on beige body
- 75 mg: stylized "A" on beige cap and "LGX 75mg" on white body

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

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

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 BRAFTOVI in combination with binimetinib. Median time to first occurrence of cuSCC/KA was 5.8 months (range 1 to 9 months) *[see Adverse Reactions (6.1)]*.

For patients who received BRAFTOVI as a single agent, cuSCC/KA was reported in 8%, basal cell carcinoma in 1%, and a new primary melanoma in 5% of patients.

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.

Non-Cutaneous Malignancies

Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies *[see Dosage and Administration (2.3)]*.

5.2 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 BRAFTOVI *[see Indications and Usage (1), Dosage and Administration (2.1)]*.

5.3 Hemorrhage

Hemorrhage can occur when BRAFTOVI is administered in combination with binimetinib. In COLUMBUS, hemorrhage occurred in 19% of patients receiving BRAFTOVI 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.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.4 Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with BRAFTOVI in combination with binimetinib. In COLUMBUS, the incidence of uveitis among patients treated with BRAFTOVI in combination with binimetinib was 4%.

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 *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.5 QT Prolongation

BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients *[see Clinical Pharmacology (12.2)]*. In COLUMBUS, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with binimetinib.

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 BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc > 500 ms *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action, BRAFTOVI 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 women of the potential risk to a fetus. Advise females of reproductive potential to use an effective, non-hormonal method of contraception since BRAFTOVI can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the final dose of BRAFTOVI *[see Use in Specific Populations (8.1, 8.3)]*.

5.7 Risks Associated with BRAFTOVI as a Single Agent

BRAFTOVI when used as a single agent is associated with an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with binimetinib. Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% of patients treated with BRAFTOVI in combination with binimetinib *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

If binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended *[see Dosage and Administration (2.3)]*.

5.8 Risks Associated with Combination Treatment

BRAFTOVI is indicated for use in combination with binimetinib. Refer to the binimetinib prescribing information for additional risk information that applies to combination use treatment.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Uveitis *[see Warnings and Precautions (5.4)]*
- QT Prolongation *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BRAFTOVI in combination with binimetinib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS).

The COLUMBUS trial *[see Clinical Studies (14)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 msec), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 11.8 months for patients treated with BRAFTOVI in combination with binimetinib and 6.2 months for patients treated with vemurafenib.

The most common (≥ 25%) adverse reactions in patients receiving BRAFTOVI in combination with binimetinib were fatigue, nausea, vomiting, abdominal pain, and arthralgia.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with binimetinib; the most common were nausea (7%), vomiting (7%) and pyrexia (4%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 14% of patients receiving BRAFTOVI in combination with binimetinib; the most common were arthralgia (2%), fatigue (2%) and nausea (2%). Five percent (5%) of patients receiving BRAFTOVI in combination with binimetinib experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI; the most common were hemorrhage in 2% and headache in 1% of patients.

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities, respectively, identified in COLUMBUS. The COLUMBUS trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for BRAFTOVI in combination with binimetinib, as compared to vemurafenib, for any specific adverse reaction listed in Table 3.

Table 3: Adverse Reactions Occurring in ≥ 10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	6
Pyrexia[c]	18	4	30	0
Gastrointestinal Disorders				
Nausea	41	2	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	6	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	26	1	46	6
Myopathy[c]	23	0	22	1
Pain in extremity	11	1	13	1
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis[c]	23	1	49	1
Rash[c]	22	1	53	13
Dry skin[c]	16	0	26	0
Alopecia[c]	14	0	38	0
Pruritus[c]	13	1	21	1
Nervous System Disorders				
Headache[c]	22	2	20	1
Dizziness[c]	15	3	4	0
Peripheral neuropathy[c]	12	1	13	2
Vascular Disorders				
Hemorrhage[c]	19	3	9	2

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4 adverse reactions limited to fatigue (n=1), pruritus (n=1) and rash (n=1) in the BRAFTOVI with binimetinib arm.
[c] Represents a composite of multiple, related preferred terms.

BRAFTOVI when used as a single agent increases the risk of certain adverse reactions compared to BRAFTOVI in combination with binimetinib. In patients receiving BRAFTOVI 300 mg orally once daily as a single agent, the following adverse reactions were observed at a higher rate (≥ 5%) compared to patients receiving BRAFTOVI in combination with binimetinib: palmar-plantar erythrodysesthesia syndrome (51% vs. 7%), hyperkeratosis (57% vs. 23%), dry skin (38% vs. 16%), erythema (16% vs. 7%), rash (41% vs. 22%), alopecia (56% vs. 14%), pruritus (31% vs. 13%), arthralgia (44% vs. 26%), myopathy (33% vs. 23%), back pain (15% vs. 9%), dysgeusia (13% vs. 6%), and acneiform dermatitis (8% vs. 3%).

Other clinically important adverse reactions occurring in < 10% of patients who received BRAFTOVI in combination with binimetinib were:

Nervous system disorders: *Facial paresis*

Gastrointestinal disorders: *Pancreatitis*

Skin and subcutaneous tissue disorders: *Panniculitis*

Immune system disorders: *Drug hypersensitivity*

Table 4: Laboratory Abnormalities Occurring in ≥ 10% (All Grades) of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Laboratory Abnormality	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	36	3.6	34	2.2
Leukopenia	13	0	10	0.5
Lymphopenia	13	2.1	30	7
Neutropenia	13	3.1	4.8	0.5
Chemistry				
Increased Creatinine	93	3.6	92	1.1
Increased Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Hyperglycemia	28	5	20	2.7
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5
Hypermagnesemia	10	1.0	26	0.5

[a] Grades per National Cancer Institute CTCAE v4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRAFTOVI

Strong or Moderate CYP3A4 Inhibitors

Concomitant administration of BRAFTOVI with a strong or moderate CYP3A4 inhibitor increased encorafenib plasma concentrations and may increase encorafenib adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration of strong or moderate CYP3A4 inhibitors cannot be avoided, modify dose as recommended *[see Dosage and Administration (2.4)]*.

Strong or Moderate CYP3A4 Inducers

Concomitant administration of BRAFTOVI with a strong or moderate CYP3A4 inducer may decrease encorafenib plasma concentrations and may decrease encorafenib efficacy *[see Clinical Pharmacology (12.3)]*. Avoid concomitant administration of strong or moderate CYP3A4 inducers with BRAFTOVI.

7.2 Effect of BRAFTOVI on Other Drugs

Sensitive CYP3A4 Substrates

Concomitant administration of BRAFTOVI with sensitive CYP3A4 substrates may result in increased toxicity or decreased efficacy of these agents.

Coadministration of BRAFTOVI with hormonal contraceptives (CYP3A4 substrates) can result in decreased concentrations and loss of hormonal contraceptive efficacy. Avoid hormonal contraceptives *[see Use in Specific Populations (8.3)]*.

7.3 Drugs That Prolong the QT Interval

BRAFTOVI is associated with dose-dependent QTc interval prolongation. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval *[see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available clinical data on the use of BRAFTOVI during pregnancy. In animal reproduction studies, 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 clinical dose of 450 mg, with no clear findings at lower doses *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In reproductive toxicity studies, administration of encorafenib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights, and increased incidence of total skeletal variations at a dose of 20 mg/kg/day (approximately 26 times the human exposure based on area under the concentration-time curve [AUC] at the recommended clinical dose of 450 mg once daily). In pregnant rabbits, administration of encorafenib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, increased incidence of total skeletal variations and increased post-implantation loss, including total loss of pregnancy at a dose of 75 mg/kg/day (approximately 178 times the human exposure based on AUC at the recommended clinical dose of 450 mg once daily). While formal placental transfer studies have not been performed, encorafenib exposure in the fetal plasma of both rats and rabbits was up to 1.7% and 0.8%, respectively, of maternal exposure.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating BRAFTOVI *[see Use in Specific Populations (8.1)]*.

Contraception

BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with BRAFTOVI and for 2 weeks after the final dose. Counsel patients to use a non-hormonal method of contraception since BRAFTOVI has the potential to render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Infertility

Males

Based on findings in male rats at doses approximately 13 times the human exposure at the 450 mg clinical dose, use of BRAFTOVI may impact fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of BRAFTOVI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI at doses between 300 mg and 600 mg once daily in combination with binimetinib (45 mg twice daily) across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib were observed in elderly patients as compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Dose adjustment for BRAFTOVI is not recommended in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been established for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

8.7 Renal Impairment

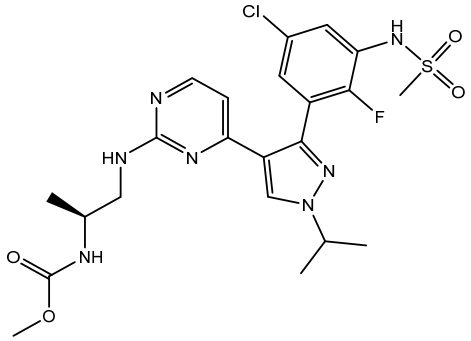
No dose adjustment is recommended for patients with mild to moderate renal impairment (CLcr 30 to < 90 mL/min) *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been established for patients with severe renal impairment (CLcr < 30 mL/min).

10 OVERDOSAGE

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

11 DESCRIPTION

Encorafenib is a kinase inhibitor. The chemical name is methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate. The molecular formula is $C_{22}H_{27}ClFN_7O_4S$ and the molecular weight is 540 daltons. The chemical structure of encorafenib is shown below:



Encorafenib is a white to almost white powder. In aqueous media, encorafenib is slightly soluble at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and higher.

BRAFTOVI (encorafenib) capsules for oral use contain 50 mg or 75 mg of encorafenib with the following inactive ingredients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable origin). The capsule shell contains gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (pharmaceutical glaze, ferrosoferric oxide, propylene glycol).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Encorafenib is a kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF in in vitro cell-free assays with IC_{50} values of 0.35, 0.47, and 0.3 nM, respectively. Mutations in the BRAF gene, such as BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Encorafenib was also able to bind to other kinases in vitro including JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, and STK36 and substantially reduce ligand binding to these kinases at clinically achievable concentrations (≤ 0.9 μM).

Encorafenib inhibited in vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. In mice implanted with tumor cells expressing BRAF V600E, encorafenib induced tumor regressions associated with RAF/MEK/ERK pathway suppression.

Encorafenib and binimetinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, co-administration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in BRAF V600E mutant human melanoma xenograft studies in mice. Additionally, the combination of encorafenib and binimetinib delayed the emergence of resistance in BRAF V600E mutant human melanoma xenografts in mice compared to either drug alone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associated with dose-dependent QTc interval prolongation. Following administration of the recommended dose of BRAFTOVI in combination with binimetinib, based on a central tendency analysis of QTc in a study of adult patients with melanoma, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms *[see Warnings and Precautions (5.5)]*.

12.3 Pharmacokinetics

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg. After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg. Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1; intersubject variability (CV%) of AUC ranged from 12% to 69%.

Absorption

After oral administration, the median T_{max} of encorafenib is 2 hours. At least 86% of the dose is absorbed.

Effect of Food

Administration of a single dose of BRAFTOVI 100 mg (0.2 times the recommended dose) with a high-fat, high-calorie meal (comprised of approximately 150 calories from protein, 350 calories from carbohydrates, and 500 calories from fat) decreased the mean maximum encorafenib concentration (C_{max}) by 36% with no effect on AUC.

Distribution

Encorafenib is 86% bound to human plasma proteins in vitro. The blood-to-plasma concentration ratio is 0.58. The geometric mean (CV%) of apparent volume of distribution is 164 L (70%).

Elimination

The mean (CV%) terminal half-life ($t_{1/2}$) of encorafenib is 3.5 hours (17%), and the apparent clearance is 14 L/h (54%) at day 1, increasing to 32 L/h (59%) at steady-state.

Metabolism

The primary metabolic pathway is N-dealkylation, with CYP3A4 as the main contributor (83%) to total oxidative clearance of encorafenib in human liver microsomes, followed by CYP2C19 (16%) and CYP2D6 (1%).

Excretion

Following a single oral dose of 100 mg radiolabeled encorafenib, 47% (5% unchanged) of the administered dose was recovered in the feces and 47% (2% unchanged) was recovered in the urine.

Specific Populations

Age (19 to 89 years), sex, body weight, mild hepatic impairment (Child-Pugh Class A), and mild or moderate renal impairment (CLcr 30 to < 90 mL/min) do not have a clinically meaningful effect on the pharmacokinetics of encorafenib. The effect of race or ethnicity, moderate or severe hepatic impairment (Child-Pugh Class B or C), and severe renal impairment (CLcr < 30 mL/min) on encorafenib pharmacokinetics have not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A4 Inhibitors on Encorafenib: Coadministration of a strong (posaconazole) or moderate (diltiazem) CYP3A4 inhibitor with BRAFTOVI increased the AUC of encorafenib by 3- and 2-fold, respectively, and increased the C_{max} by 68% and 45%, respectively, after a single BRAFTOVI dose of 50 mg (0.1 times the recommended dose).

Effect of CYP3A4 Inducers on Encorafenib: The effect of coadministration of a CYP3A4 inducer on encorafenib exposure has not been studied. In clinical trials, steady-state encorafenib exposures were lower than encorafenib exposures after the first dose, suggesting CYP3A4 auto-induction.

Effect of Acid Reducing Agents on Encorafenib: Coadministration of a proton pump inhibitor, rabeprazole, had no effect on AUC and C_{max} of encorafenib.

Combination Treatment: Coadministration of BRAFTOVI (UGT1A1 inhibitor) with binimetinib (UGT1A1 substrate) had no effect on binimetinib exposure.

In Vitro Studies

Effect of Encorafenib on CYP/UGT Substrates: Encorafenib is a reversible inhibitor of UGT1A1, CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, and CYP3A, and a time-dependent inhibitor of CYP3A4 at clinically relevant plasma concentrations. Encorafenib induced CYP2B6, CYP2C9, and CYP3A4 at clinically relevant plasma concentrations.

Effect of Transporters on Encorafenib: Encorafenib is a substrate of P-glycoprotein (P-gp). Encorafenib is not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide (OATP1B1, OATP1B3) or organic cation transporter (OCT1) at clinically relevant plasma concentrations.

Effect of Encorafenib on Transporters: Encorafenib inhibited P-gp, BCRP, OCT2, organic anion transporter (OAT1, OAT3), OATP1B1, and OATP1B3, but not OCT1 or MRP2 at clinically relevant plasma concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with encorafenib have not been conducted. Encorafenib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

No dedicated fertility studies were performed with encorafenib in animals. In a general toxicology study in rats, decreased testes and epididymis weights, tubular degeneration in testes, and oligospermia in epididymides were observed at doses approximately 13 times the human exposure at the 450 mg clinical dose based on AUC. No effects on reproductive organs were observed in either sex in any of the non-human primate toxicity studies.

13.2 Animal Toxicology and/or Pharmacology

Adverse histopathology findings of hyperplasia and hyperkeratosis occurred in the stomach of rats at encorafenib doses of 20 mg/kg/day (approximately 14 times the human exposure at the 450 mg clinical dose based on AUC) or greater, in both 4 and 13-week studies.

14 CLINICAL STUDIES

BRAFTOVI in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Randomization was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and prior immunotherapy for unresectable or metastatic disease (yes versus no).

Patients were randomized (1:1:1) to receive BRAFTOVI 450 mg once daily in combination with binimetinib 45 mg twice daily (BRAFTOVI in combination with binimetinib), BRAFTOVI 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved dosing (BRAFTOVI 450 mg in combination with binimetinib 45 mg) are described below.

The major efficacy outcome measure was progression-free survival (PFS) of BRAFTOVI in combination with binimetinib compared with vemurafenib as assessed by a blinded independent central review. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurred first. Other outcome measures included overall survival (OS), objective response rate (ORR), and duration of response (DoR) as assessed by central review.

A total of 577 patients were randomized, 192 to the BRAFTOVI in combination with binimetinib arm, 194 to the BRAFTOVI arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the BRAFTOVI in combination with binimetinib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Ninety-five percent (95%) had metastatic disease, 65% were Stage IVM1c, and 4% received prior CTLA-4, PD-1, or PD-L1 directed antibodies. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥ 3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%).

BRAFTOVI in combination with binimetinib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 5 and Figure 1.

Table 5: Efficacy Results for COLUMBUS

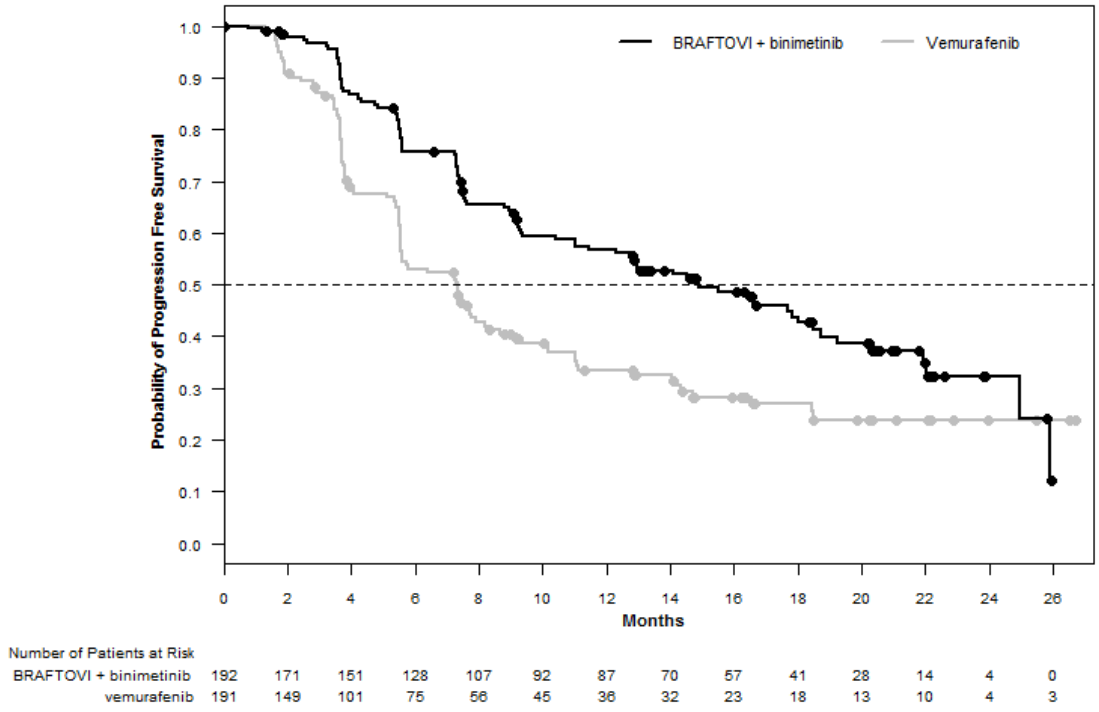
	BRAFTOVI with binimetinib N=192	Vemurafenib N=191
Progression-Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS, months (95% CI)	14.9 (11, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)[a]	0.54 (0.41, 0.71)	
P-value[b]	<0.0001	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		
Median DoR, months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; PFS = Progression-free survival; PR = Partial response.

[a] Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

[b] Log-rank test adjusted by the same stratification factors.

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in COLUMBUS



OS was not mature at the time of analysis of PFS.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRAFTOVI (encorafenib) is supplied as 50 mg and 75 mg hard gelatin capsules.

50 mg: stylized "A" on orange cap and "LGX 50mg" on beige body, available in cartons (NDC 70255-020-01) containing two bottles of 60 capsules each (NDC 70255-020-02).

75 mg: stylized “A” on beige cap and “LGX 75mg” on white body, available in cartons (NDC 70255-025-01) containing two bottles of 90 capsules each (NDC 70255-025-02).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Do not use if safety seal under cap is broken or missing. Dispense in original bottle. Do not remove desiccant. Protect from moisture. Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the following:

New Primary Cutaneous Malignancies

Advise patients to contact their healthcare provider immediately for change in or development of new skin lesions *[see Warnings and Precautions (5.1)]*.

Hemorrhage

Advise patients to notify their healthcare provider immediately with any symptoms suggestive of hemorrhage, such as unusual bleeding *[see Warnings and Precautions (5.3)]*.

Uveitis

Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.4)]*.

QT Prolongation

Advise patients that BRAFTOVI can cause QTc interval prolongation and to inform their physician if they have any QTc interval prolongation symptoms, such as syncope [*see Warnings and Precautions (5.5)*].

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity: Advise females with reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with BRAFTOVI and for 2 weeks after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with BRAFTOVI *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1)]*.

Lactation: Advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility: Advise males of reproductive potential that BRAFTOVI may impair fertility *[see Use in Specific Populations (8.3)]*.

Strong or Moderate CYP3A Inducers or Inhibitors

Coadministration of BRAFTOVI with a strong or moderate CYP3A inhibitor may increase encorafenib concentrations; while coadministration of BRAFTOVI with a strong or moderate CYP3A inducer may decrease encorafenib concentrations. Advise patients that they need to avoid certain medications while taking BRAFTOVI and to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit or grapefruit juice while taking BRAFTOVI [*see Drug Interactions (7.1)*].

Storage

BRAFTOVI is moisture sensitive. Advise patients to store BRAFTOVI in the original bottle with desiccant and to keep the cap of the bottle tightly closed. Do not remove the desiccants from the bottle.

Distributed by:

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