BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

IMPORTANT SAFETY INFORMATION for BRAFTOVI and MEKTOVI (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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 exposed to BRAF inhibitors. Confirm evidence of *BRAF V600E* or *V600K* mutation using an FDA-approved test prior to initiating BRAFTOVI.

Cardiomyopathy: Cardiomyopathy manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the PHAROS trial, evidence of cardiomyopathy occurred in 11% and Grade 3 left ventricular dysfunction occurred in 1% of patients. Cardiomyopathy resolved in 82% of patients. Assess left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated acquisition (MUGA) scan prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment. The safety has not been established in patients with a 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity: Hepatotoxicity can occur when MEKTOVI is administered in combination with BRAFTOVI. In the PHAROS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests was 10% for aspartate aminotransferase (AST), 9% for alanine aminotransferase (ALT), and 3.2% for alkaline phosphatase. Monitor liver laboratory tests before initiation of BRAFTOVI and MEKTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Rhabdomyolysis: Rhabdomyolysis can occur when MEKTOVI is administered in combination with BRAFTOVI. In the PHAROS trial, elevation of laboratory values of serum creatine kinase (CK) occurred in 41% of patients. No patient experienced rhabdomyolysis. Monitor CPK and creatinine levels prior to initiating MEKTOVI, periodically during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the PHAROS trial, hemorrhage occurred in 12% of patients, including fatal intracranial hemorrhage (1%); Grade 3 or 4 hemorrhage occurred in 4.1% of patients. The most frequent hemorrhagic events were anal hemorrhage and hemothorax (2% each). Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Venous Thromboembolism (VTE): In the PHAROS trial, VTE occurred in 7% of patients, including 1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Ocular Toxicities: In the PHAROS trial, serous retinopathy (retinal detachment) occurred in 2% of patients with no cases of blindness. Retinal vein occlusion (RVO) is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with BRAFTOVI. The safety of MEKTOVI has not been established in patients with a history of RVO or current risk factors for RVO including uncontrolled glaucoma or a history of hyperviscosity or hypercoagulability syndromes. Perform ophthalmological evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO. Uveitis, including iritis and iridocyclitis, was

WARNINGS AND PRECAUTIONS (cont'd)

Ocular Toxicities (cont'd)
reported in patients treated with MEKTOVI in combination with BRAFTOVI. In PHAROS, uveitis occurred in 1% of patients. Assess for visual symptoms at each visit. Perform an ophthalmological 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: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the PHAROS trial, an increase in QTcF to >500 ms was measured in 2.1% (2/95) of patients who received BRAFTOVI with MEKTOVI. 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.

Interstitial Lung Disease (ILD): In the PHAROS trial, 1 patient (1%) receiving MEKTOVI with BRAFTOVI developed pneumonitis. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Embryo-Fetal Toxicity: BRAFTOVI and MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Effective, non-hormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI with MEKTOVI.

Risks Associated with BRAFTOVI as a Single Agent: There is an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

Risks Associated with Combination Treatment: BRAFTOVI is indicated for use as part of a regimen in combination with MEKTOVI. Refer to the prescribing information for BRAFTOVI and MEKTOVI for additional risk information.

Lactation: Advise women not to breastfeed during treatment with BRAFTOVI and MEKTOVI and for 2 weeks after the final dose.

Infertility: Advise males of reproductive potential that BRAFTOVI may impair fertility.

ADVERSE REACTIONS

The most common adverse reactions (≥25%, all grades, in the PHAROS trial) for BRAFTOVI with MEKTOVI were: fatigue (61%), nausea (58%), diarrhea (52%), musculoskeletal pain (48%), vomiting (37%), abdominal pain (32%), visual impairment (29%), constipation (27%), dyspnea (27%), rash (27%), and cough (26%).

Serious adverse reactions occurred in 38% of patients receiving BRAFTOVI with MEKTOVI. Serious adverse reactions (≥2% of patients in the PHAROS trial) were hemorrhage (6%), diarrhea (4.1%), anemia (3.1%), dyspnea (3.1%), pneumonia (3.1%), arrhythmia (2%), device related infection (2%), edema (2%), myocardial

Please see additional Important Safety Information on pages 1 and 4 and full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI in the pocket for additional information. For more information, please visit BraftoviMektoviHCP.com/n.

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IMPORTANT SAFETY INFORMATION for BRAFTOVI and MEKTOVI (cont'd)

ADVERSE REACTIONS (cont'd)

infarction (2%), and pleural effusion (2%). Fatal adverse reactions occurred in 2% of patients, including intracranial hemorrhage (1%) and myocardial infarction (1%).

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI with MEKTOVI in the PHAROS trial were peripheral neuropathy, dysgeusia, facial paresis, pancreatitis, hyperkeratosis, erythema, photosensitivity, and drug hypersensitivity.

In the PHAROS trial, the most common laboratory abnormalities (all grades) (≥20%) for BRAFTOVI and MEKTOVI included increased creatinine (91%), hyperglycemia (48%), anemia (47%), increased creatine kinase (41%), lipase increased (40%), increased ALT (34%), hypoalbuminemia (32%), increased alkaline phosphatase (31%), increased AST (31%), hyperkalemia (31%), hyponatremia (26%), lymphopenia (24%), serum amylase increased (22%), and thrombocytopenia (20%).

DRUG INTERACTIONS

Strong or moderate CYP3A4 inhibitors: Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose.

DRUG INTERACTIONS (cont'd)

Strong CYP3A4 inducers: Avoid coadministration of BRAFTOVI with strong CYP3A4 inducers.

Sensitive CYP3A4 substrates: Avoid the coadministration of BRAFTOVI with CYP3A4 substrates (including hormonal contraceptives) 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.

Dose reductions of drugs that are **substrates of OATP1B1, OATP1B3, or BCRP** may be required when used concomitantly with BRAFTOVI.

Avoid coadministration of BRAFTOVI with **drugs known to prolong QT/QTc interval.**

Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI in the pocket for additional information. For more information, please visit BraftoviMektoviHCP.com/n.

FALL NATIONAL SPEAKER SERIES

In Support of Lung Cancer Awareness Month

LORBRENA® LORLATINIB 100 mg | 25 mg tablets

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Join us virtually to learn more about LORBRENA and BRAFTOVI + MEKTOVI, and deepen your understanding about key data.*

Eric Nadler, MD
Medical Oncologist
Texas Oncology

Scan the QR code to register.

Session 1:
Thursday, November 6
1:15 PM–2:00 PM EST
10:15 AM–11:00 AM PST

Session 2:
Thursday, November 6
3:15 PM–4:00 PM EST
12:15 PM–1:00 PM PST

Sarah Sagorsky, MPAS, PA-C
Physician Assistant
Johns Hopkins

Scan the QR code to register.

Session 3:
Tuesday, November 11
12:15 PM–1:00 PM EST
9:15 AM–10:00 AM PST

Session 4:
Wednesday, November 19
2:15 PM–3:00 PM EST
11:15 AM–12:00 PM PST

*Presentation is non-CME and is not eligible for AMA PRA Category 1 credit. Speakers will be presenting the information virtually.

INDICATION for LORBRENA

LORBRENA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

Information on FDA-approved tests for the detection of *ALK* rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics.

IMPORTANT SAFETY INFORMATION for LORBRENA

Contraindications: LORBRENA is contraindicated in patients taking strong CYP3A inducers, due to the potential for serious hepatotoxicity.

Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers: Severe hepatotoxicity occurred in 10 of 12 healthy subjects receiving a single dose of LORBRENA with multiple daily doses of rifampin, a strong CYP3A inducer. Grade 4 ALT or AST elevations occurred in 50% of subjects, Grade 3 in 33% of subjects, and Grade 2 in 8% of subjects. ALT or AST elevations occurred within 3 days and returned to within normal limits after a median of 15 days (7 to 34 days); median time to recovery in subjects with Grade 3 or 4 or Grade 2 ALT or AST elevations was 18 days and 7 days, respectively. LORBRENA is contraindicated in patients taking strong CYP3A inducers. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating LORBRENA.

Please see additional Important Safety Information on page 2 and full Prescribing Information in pocket. For more information, please visit LorbrenaHCP.com.

INDICATION AND USAGE for BRAFTOVI and MEKTOVI

BRAFTOVI and MEKTOVI are kinase inhibitors indicated for use in combination for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a *BRAF V600E* mutation, as detected by an FDA-approved test.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF NSCLC.

IMPORTANT SAFETY INFORMATION for BRAFTOVI and MEKTOVI

The information below applies to the safety of the combination of BRAFTOVI and MEKTOVI unless otherwise noted. See full Prescribing Information for BRAFTOVI and for MEKTOVI for dose modifications for adverse reactions.

WARNINGS AND PRECAUTIONS

New Primary Malignancies: New primary malignancies, cutaneous and non-cutaneous, can occur. In the PHAROS trial, cutaneous squamous cell carcinoma (cuSCC) and skin papilloma (SP), each occurred in 2% 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. Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies. Monitor patients for new malignancies prior to initiation of treatment, while on treatment, and after discontinuation of treatment.

Please see additional Important Safety Information on pages 3-4 and full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI in the pocket for additional information. For more information, please visit BraftoviMektoviHCP.com/n.

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Project: LORBRENA VIRTUAL SPEAKER FLYER
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PFIZER_BU_ONCOLOGY_COLOR_CMYK.EPS, DOCK_728X90_INSIDE.TIF (CMYK; 666 PPI), BRAFTOVI_MEKTOVI_R_CMYK#02.AI, LORBRENA-DOSAGE_100MG_25MG_SMALL_4C_1.AI, ERIC_NADLER_4C.TIF (CMYK; 555 PPI), SARAH_SAGORSKY_4C.TIF (CMYK; 1488 PPI), SESSION1_NQO.AI, SESSION2_NDC.AI, SESSION3_NQZ.AI, SESSION4_NQD.AI

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B2045-006367-00
Shipping Date: SEPT. 16, 2025
Modified: 9-18-2025 10:13 AM
Workstation: SHAHID QURESHI

Scale: 1" = 1"
Built at %: 100%
Output at %: 100%
Minimum DPI: 300
Safety: NONE
V.O.: NONE
Trim: 25.375" X 11"
Bleed: 25.875" X 11.5"
Colour: 4/4

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IMPORTANT SAFETY INFORMATION for LORBRENA (cont'd)

Central Nervous System (CNS) Effects: A broad spectrum of CNS effects can occur; overall, CNS effects occurred in 52% of the 476 patients receiving LORBRENA. These included seizures (1.9%, sometimes in conjunction with other neurologic findings), psychotic effects (7%; 0.6% severe [Grade 3 or 4]), and changes in cognitive function (28%; 2.9% severe), mood (including suicidal ideation) (21%; 1.7% severe), speech (11%; 0.6% severe), mental status (1.3%; 1.1% severe), and sleep (12%). Median time to first onset of any CNS effect was 1.4 months (1 day to 3.4 years). Overall, 2.1% and 10% of patients required permanent or temporary discontinuation of LORBRENA, respectively, for a CNS effect; 8% required dose reduction. Withhold and resume at same or reduced dose or permanently discontinue based on severity.

Hyperlipidemia: Increases in serum cholesterol and triglycerides can occur. Grade 3 or 4 elevations in total cholesterol occurred in 18% and Grade 3 or 4 elevations in triglycerides occurred in 19% of the 476 patients who received LORBRENA. Median time to onset was 15 days for both hypercholesterolemia and hypertriglyceridemia. Approximately 4% and 7% of patients required temporary discontinuation and 1% and 3% of patients required dose reduction of LORBRENA for elevations in cholesterol and in triglycerides in Study B7461001 and Study B7461006, respectively. Eighty-three percent of patients required initiation of lipid-lowering medications, with a median time to onset of start of such medications of 17 days. Initiate or increase the dose of lipid-lowering agents in patients with hyperlipidemia. Monitor serum cholesterol and triglycerides before initiating LORBRENA, 1 and 2 months after initiating LORBRENA, and periodically thereafter. Withhold and resume at same dose for the first occurrence; resume at same or reduced dose of LORBRENA for recurrence based on severity.

Atrioventricular (AV) Block: PR interval prolongation and AV block can occur. In 476 patients who received LORBRENA at a dose of 100 mg orally once daily and who had a baseline electrocardiography (ECG), 1.9% experienced AV block and 0.2% experienced Grade 3 AV block and underwent pacemaker placement. Monitor ECG prior to initiating LORBRENA and periodically thereafter. Withhold and resume at reduced or same dose in patients who undergo pacemaker placement. Permanently discontinue for recurrence in patients without a pacemaker.

Interstitial Lung Disease (ILD)/Pneumonitis: Severe or life-threatening pulmonary adverse reactions consistent with ILD/pneumonitis can occur. ILD/pneumonitis occurred in 1.9% of patients, including Grade 3 or 4 ILD/pneumonitis in 0.6% of patients. Four patients (0.8%) discontinued LORBRENA for ILD/pneumonitis. Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever). Immediately withhold LORBRENA in patients with suspected ILD/pneumonitis. Permanently discontinue LORBRENA for treatment-related ILD/pneumonitis of any severity.

Hypertension: Hypertension can occur. Hypertension occurred in 13% of patients, including Grade 3 or 4 in 6% of patients. Median time to onset of hypertension was 6.4 months (1 day to 2.8 years), and 2.3% of patients temporarily discontinued LORBRENA for hypertension. Control blood pressure prior to initiating LORBRENA. Monitor blood pressure after 2 weeks and at least monthly thereafter. Withhold and resume at reduced dose or permanently discontinue based on severity.

Hyperglycemia: Hyperglycemia can occur. Hyperglycemia occurred in 9% of patients, including Grade 3 or 4 in 3.2% of patients. Median time to onset of hyperglycemia was 4.8 months (1 day to 2.9 years), and 0.8% of patients temporarily discontinued LORBRENA for hyperglycemia. Assess fasting serum glucose prior to initiating LORBRENA and monitor periodically thereafter. Withhold and resume at reduced dose or permanently discontinue based on severity.

Embryo-fetal Toxicity: LORBRENA can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective non-hormonal method of contraception, since LORBRENA can render hormonal contraceptives ineffective, during treatment with LORBRENA and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with LORBRENA and for 3 months after the final dose.

Adverse Reactions: In the pooled safety population of 476 patients who received 100 mg LORBRENA once daily, the most frequent (≥ 20%) adverse reactions were edema (56%), peripheral neuropathy (44%), weight gain (31%), cognitive effects (28%), fatigue (27%), dyspnea (27%), arthralgia (24%), diarrhea (23%), mood effects (21%), and cough (21%). The most frequent (≥ 20%) Grade 3-4 laboratory abnormalities in patients receiving LORBRENA were hypercholesterolemia (21%) and hypertriglyceridemia (21%).

In previously untreated patients, serious adverse reactions occurred in 34% of the 149 patients treated with LORBRENA; the most frequently reported serious adverse reactions were pneumonia (4.7%), dyspnea (2.7%), respiratory failure (2.7%), cognitive effects (2.0%), and pyrexia (2.0%). Fatal adverse reactions occurred in 3.4% of patients and included pneumonia (0.7%), respiratory failure (0.7%), cardiac failure acute (0.7%), pulmonary embolism (0.7%), and sudden death (0.7%). In the Phase 1/2 study, serious adverse reactions occurred in 32% of the 295 patients; the most frequently reported serious adverse reactions were pneumonia (3.4%), dyspnea (2.7%), pyrexia (2%), mental status changes (1.4%), and respiratory failure (1.4%). Fatal adverse reactions occurred in 2.7% of patients and included pneumonia (0.7%), myocardial infarction (0.7%), acute pulmonary edema (0.3%), embolism (0.3%), peripheral artery occlusion (0.3%), and respiratory distress (0.3%).

Drug Interactions: LORBRENA is contraindicated in patients taking strong CYP3A inducers. Avoid concomitant use with moderate CYP3A inducers, strong CYP3A inhibitors, and fluconazole. If concomitant use of moderate CYP3A inducers cannot be avoided, increase the LORBRENA dose as recommended. If concomitant use with a strong CYP3A inhibitor or fluconazole cannot be avoided, reduce the LORBRENA dose as recommended. Avoid concomitant use of LORBRENA with CYP3A substrates and P-gp substrates, which may reduce the efficacy of these substrates.

Lactation: Because of the potential for serious adverse reactions in breastfed infants, instruct women not to breastfeed during treatment with LORBRENA and for 7 days after the final dose.

Hepatic Impairment: No dose adjustment is recommended for patients with mild hepatic impairment. The recommended dose of LORBRENA has not been established for patients with moderate or severe hepatic impairment.

Renal Impairment: Reduce the dose of LORBRENA for patients with severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment.

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