STRATEGIES FOR
MANAGING PYREXIA
IN YOUR PATIENTS TAKING TAFINLAR + MEKINIST

INDICATION
TAFINLAR® (dabrafenib), in combination with MEKINIST® (trametinib), is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

Limitation of Use: TAFINLAR is not indicated for the treatment of patients with wild-type BRAF melanoma. MEKINIST is not indicated for treatment of patients who have progressed on prior BRAF-inhibitor therapy.

IMPORTANT SAFETY INFORMATION
New Primary Malignancies. New primary malignancies, cutaneous and noncutaneous, can occur.

Cutaneous Malignancies: In the COMBI-d study, the incidence of cutaneous malignancies in patients receiving TAFINLAR in combination with MEKINIST (the combination) compared with patients receiving TAFINLAR as a single agent was as follows: basal cell carcinoma 3.3% (7/209) vs 6% (13/211); cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma 3% vs 10%; new primary melanoma 0.5% (1/209) vs 1.9% (4/211).

The median time to first diagnosis of basal cell carcinoma was 5.1 months (range: 2.8-23.9 months) in patients receiving the combination and 4.4 months (range: 29 days-16.5 months) in patients receiving TAFINLAR as a single agent. Among the 7 patients receiving the combination that developed basal cell carcinoma, 2 (29%) experienced more than 1 occurrence (range: 1-3).

The median time to first diagnosis of cuSCC was 7.3 months (range: 1.8-16.8 months) in patients receiving the combination and 2 months (range: 9 days-20.9 months) in patients receiving TAFINLAR as a single agent. Perform dermatologic evaluations prior to initiation of therapy, every 2 months while on therapy and for up to 6 months following discontinuation of TAFINLAR. No dose modifications are required in patients who develop new primary cutaneous malignancies.
PYREXIA WAS THE MOST COMMON ADVERSE REACTION OBSERVED WITH TAFINLAR + MEKINIST\(^1,2\)

54\% of patients experienced pyrexia across two phase 3 clinical trials\(^1,2\)

- Grade 3 pyrexia was observed in 5\% of all patients (n=27/559)\(^1,4\)
- Grade 4 pyrexia was not observed (n=0/559)\(^1,3\)

Of patients who experienced pyrexia\(^1,4\):

\[91\% \text{ grade 1 or 2 pyrexia} \quad (n=276/303)\]
\[9\% \text{ grade 3 pyrexia} \quad (n=27/303)\]

54\% any-grade pyrexia (n=303/559)

1.4\% TO 1.9\% OF PATIENTS DISCONTINUED TREATMENT DUE TO PYREXIA ACROSS BOTH PHASE 3 CLINICAL TRIALS\(^1,2\)

- Approximately one-half of the patients who experienced pyrexia had 3 or more discrete events\(^1,2\)
- The incidence of fever (serious and nonserious) in patients treated with TAFINLAR\(^\circledR\) (dabrafenib) + MEKINIST\(^\circledR\) (trametinib) in COMBI-d and COMBI-v was 54\% (303/559). Serious febrile reactions or fever of any severity complicated by severe rigors/chills, hypotension, dehydration, renal failure, or syncope occurred in 17\% (93/559) of patients receiving TAFINLAR + MEKINIST. Fever was complicated by severe chills/rigors in 0.4\% (2/559), dehydration in 1.8\% (10/559), renal failure in 0.5\% (3/559), and syncope in 0.7\% (4/559) of patients\(^1,2\)

IMPORTANT SAFETY INFORMATION (CONTINUED)

Noncutaneous Malignancies: In the COMBI-d study, noncutaneous malignancies occurred in 1.4\% (3/209) of patients who received the combination and in 2.8\% (6/211) of patients who received TAFINLAR as a single agent. Monitor patients closely for signs or symptoms of noncutaneous malignancies. Permanently discontinue TAFINLAR for RAS-mutation-positive noncutaneous malignancies. No dose modification of MEKINIST is required for patients who develop noncutaneous malignancies.

Tumor Promotion in BRAF Wild-type Melanoma. In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells that are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of therapy.

Hemorrhage. Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur. In the COMBI-d study, the incidence of hemorrhagic events in patients treated with the combination compared with TAFINLAR as a single agent was 19\% (40/209) vs 15\% (32/211), respectively. Gastrointestinal hemorrhage occurred in 6\% of 209 patients treated with the combination compared with 3\% of 211 patients treated with TAFINLAR alone. Intracranial hemorrhage was fatal in 1.4\% of 209 patients receiving the combination compared with no patients receiving TAFINLAR as a single agent.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Permanently discontinue TAFINLAR and MEKINIST for all grade 4 hemorrhagic events, and for any persistent grade 3 hemorrhagic events. Withhold the combination for grade 3 hemorrhagic events; if improved, resume at a lower dose.

Colitis and Gastrointestinal Perforation. Colitis and gastrointestinal perforation, including fatal outcomes, can occur. Across clinical trials of MEKINIST administered as a single agent (N=329) and in combination with TAFINLAR (N=559), colitis occurred in 0.6\% of patients and gastrointestinal perforation occurred in 0.3\% of patients, respectively.

Monitor patients closely for colitis and gastrointestinal perforations.
RECOMMENDED DOSE MODIFICATIONS FOR TAFINLAR AND MEKINIST ADMINISTERED IN COMBINATION1,2

Severity of Adverse Reaction*  TAFINLAR® (dabrafenib)b  MEKINIST® (trametinib)b

Febrile Drug Reaction
- Fever of 101.3°F-104°F
  - Withhold TAFINLAR until fever resolves. Then resume at same or lower dose level.
- Fever of >104°F
  - Withhold TAFINLAR until fever resolves. Then resume at a lower dose level
- Fever complicated by rigors, hypotension, dehydration, or renal failure
  - Withhold TAFINLAR until fever resolves. Then resume MEKINIST at same or lower dose level.

Cutaneous Drug Reaction
- Intolerable grade 2 skin toxicity
  - Withhold TAFINLAR for up to 3 weeks
- Grade 3 or 4 skin toxicity
  - Withhold MEKINIST for up to 3 weeks
  - If improved, resume at a lower dose level
  - If not improved, permanently discontinue TAFINLAR

Cardiac Drug Reaction
- Asymptomatic, absolute decrease in left ventricular ejection fraction (LVEF) of ≥10% from baseline and below the institutional lower limits of normal (LLN) from pretreatment value
  - Do not modify the dose of TAFINLAR.
- Symptomatic congestive heart failure
  - Withhold TAFINLAR, if improved, then resume at the same dose.
- Absolute decrease in LVEF of >20% from baseline that is below LLN
  - Permanently discontinue MEKINIST.

Venous Thromboembolism
- Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)
  - Do not modify the dose of TAFINLAR.
- Life-threatening PE
  - Permanently discontinue TAFINLAR.
  - Permanently discontinue MEKINIST.

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
*See back cover for recommended dose reductions of TAFINLAR and MEKINIST.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Venous Thromboembolism. In the COMBI-d study, deep venous thrombosis (DVT) and pulmonary embolism (PE) occurred in 2.8% of 209 patients treated with the combination vs 0.9% of 211 patients treated with TAFINLAR as a single agent.

Advis patients to immediately seek medical care if they develop symptoms of DVT or PE such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEKINIST and TAFINLAR for life-threatening PE. Withhold MEKINIST and TAFINLAR for uncomplicated DVT or PE for up to 3 weeks. If improved, MEKINIST may be resumed at a lower dose.

Cardiomyopathy. Cardiomyopathy, including cardiac failure, can occur. In the COMBI-d study, cardiomyopathy (defined as a decrease in left ventricular ejection fraction [LVEF] ≥10% from baseline and below the institutional lower limit of normal [LLN]) occurred in 6% (12/206) of patients treated with the combination and in 2.9% (6/207) of patients treated with TAFINLAR alone. The median time to onset of cardiomyopathy in patients treated with the combination was 8.2 months (range: 28 days–24.9 months), and was 4.4 months (range: 28 days–19.1 months) in patients treated with TAFINLAR as a single agent.

Cardiomyopathy was identified within the first month of treatment with the combination in 2 of 12 patients, and in 2 of 6 patients treated with TAFINLAR as a single agent. Development of cardiomyopathy resulted in dose interruption of TAFINLAR (4.4%) or discontinuation of TAFINLAR (1.0%) of patients receiving the combination and in dose interruption (2.4%), dose reduction (0.5%), or discontinuation (1.0%) of patients receiving TAFINLAR as a single agent. Cardiomyopathy resolved in 10 of 12 patients receiving the combination and in 3 of 6 patients receiving TAFINLAR as a single agent.

Assess LVEF by an echocardiogram or a multigated acquisition (MUGA) scan before initiation of therapy, 1 month after initiation then at 2- to 3-month intervals while on treatment. Withhold MEKINIST for up to 4 weeks, and continue TAFINLAR at the same dose if absolute LVEF value decreases by 10% from pretreatment values and is <LLN. For symptomatic cardiomyopathy or persistent asymptomatic LV dysfunction of ≥20% from baseline that is below LLN that does not resolve within 4 weeks, permanently discontinue MEKINIST and withhold TAFINLAR. Resume TAFINLAR at the same dose on the recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease ≤10% compared with baseline.

Ocular Toxicities. Retinal Vein Occlusion (RVO): Across all clinical trials including MEKINIST, the incidence of RVO was 0.2% (4/1749). RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Please see additional Important Safety Information for TAFINLAR and MEKINIST on the following pages. Click here for full Prescribing Information for TAFINLAR, and click here for full Prescribing Information for MEKINIST.
**IMPORTANT SAFETY INFORMATION (CONTINUED)**

Urgently (within 24 hours) perform ophthalmologic evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEKINIST in patients with documented RVO.

**Retinal Pigment Epithelial Detachment (RPED)**

RPED can occur. Retinal detachments may be bilateral and multifocal, occurring in the central macular region of the retina or elsewhere in the retina. In the COMBI-d study, routine monitoring of patients to detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is unknown. Perform ophthalmologic evaluation periodically, and at any time a patient reports visual disturbances. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmologic evaluation within 3 weeks, resume MEKINIST. Reduce the dose or discontinue MEKINIST if no improvement after 3 weeks.

**Uveitis including iritis and iridocyclitis**

- If mild or moderate uveitis does not respond to ophthalmic therapy, or for severe uveitis, withhold TAFINLAR for up to 6 weeks.
- If improved to grade 0-1, then resume at the same or at a lower dose level
- If not improved, permanently discontinue MEKINIST.

**Interstitial lung disease/pneumonitis**

- Do not modify the dose of TAFINLAR.
- Permanently discontinue MEKINIST.

**Pulmonary Drug Reaction**

 Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, and eye pain). If iritis is diagnosed, administer ophthalmic therapy and continue TAFINLAR without dose modification; for severe uveitis or iridocyclitis, interrupt TAFINLAR and treat as clinically indicated. Permanently discontinue TAFINLAR for persistent grade 2 or greater uveitis of >6 weeks duration.

**Interstitial Lung Disease (ILD).** In clinical trials of MEKINIST (N=329) as a single agent, ILD or pneumonitis occurred in 2% of patients. In the COMBI-d study, 1.0% (2/209) of patients treated with the combination developed pneumonitis compared with none of the patients receiving TAFINLAR as a single agent.

Withhold MEKINIST in patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates pending clinical investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis.

**Serious Febrile Drug Reactions.** The incidence and severity of pyrexia are increased when the combination is used compared with TAFINLAR as a single agent.

In patients treated with the combination, in the COMBI-d and COMBI-v studies, the incidence of fever was 54% (303/559) and serious febrile reactions and fever of any severity complicated by severe rigors/chills, hypotension, dehydration, renal failure, or syncope occurred in 17% (93/559). Fever was complicated by severe chills/chills in 0.4%, dehydration in 1.8%, renal failure in 0.2%, and syncope in 0.7% of 559 patients receiving the combination.

In patients treated with the combination, the median time to onset of first occurrence of fever was 1 month (range: 1 day-23.5 months) and the median duration of fever was 3 days (range: 1 day-11.3 months). About one-half of the patients on combination therapy, who experienced pyrexia, had 3 or more discrete episodes.

Withhold TAFINLAR for fever of 101.3ºF or higher. Withhold MEKINIST for fever higher than 104ºF. Withhold TAFINLAR and MEKINIST for any severe febrile reaction or fever complicated by hypotension, rigors or chills, dehydration, or renal failure, and evaluate for signs and symptoms of infection. Monitor serum creatinine and other evidence of renal function during and following severe pyrexia. Refer to the Prescribing Information for either agent for recommended dose modifications. Administer antipyretics as secondary prophylaxis when resuming TAFINLAR and/or MEKINIST if the patient had a prior episode of severe
febrile reaction or fever associated with complications. Administer corticosteroids (eg, prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications such as dehydration, hypotension, renal failure, or severe chills/ rigors, and there is no evidence of active infection.

**Serious Skin Toxicity.** Across clinical trials of the combination, serious skin toxicity occurred in 0.7% of 559 patients. In the COMBI-d study, the overall incidence of any skin toxicity was 55% for patients receiving the combination compared with 55% for patients receiving TAFINLAR® (dabrafenib) as a single agent. No serious or severe cases of skin toxicity occurred in patients treated with the combination. The median time to initial onset of skin toxicity, in patients treated with the combination, was 1.9 months (range: 1 day-22.1 months) and median time to resolution of skin toxicity was 1.2 months (range: 1 day-24.4 months). Reductions in the dose of MEKINIST® (trametinib) were required in 5% of patients receiving the combination, and no patient required permanent discontinuation of TAFINLAR or MEKINIST for skin toxicity.

Withhold TAFINLAR and MEKINIST for intolerable or severe skin toxicity. TAFINLAR and MEKINIST may be resumed at lower doses in patients with improvement or recovery from skin toxicity within 3 weeks.

**Hyperglycemia.** In the COMBI-d study, 27% of 15 patients with a history of diabetes receiving the combination and 13% of 16 patients receiving TAFINLAR as a single agent required more intensive hypoglycemic therapy. The incidence of grade 3 and grade 4 hyperglycemia based on laboratory values was 5% and 0.5% of 208 patients treated with the combination, respectively, compared with 4.3% and 0 of 209 patients treated with TAFINLAR as a single agent, respectively. Monitor serum glucose levels upon initiation, and as clinically appropriate in patients with preexisting diabetes or hyperglycemia.

**Glucose-6-Phosphate Dehydrogenase Deficiency.** TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Closely observe patients with G6PD deficiency for signs of hemolytic anemia.

**Embryo-fetal Toxicity.** TAFINLAR and MEKINIST both can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use highly effective nonhormonal contraception during treatment, and for 4 months after treatment, since TAFINLAR can render hormonal contraceptives ineffective. Advise patients to contact their health care provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR and MEKINIST.

**Most Common Adverse Reactions.** In the COMBI-d and COMBI-v studies, the most common adverse reactions (≥20%) for the combination were pyrexia (54%), nausea (35%), rash (32%), chills (31%), diarrhea (31%), headache (30%), vomiting (27%), hypertension (26%), arthralgia (25%), peripheral edema (21%), and cough (20%). In the COMBI-d and COMBI-v studies, the most common grade 3 or 4 adverse reactions (≥2%) for the combination were hypertension (11%), pyrexia (5%), and hemorrhage (2%).

**Other Clinically Important Adverse Reactions.** In the COMBI-d and COMBI-v studies, other clinically important adverse reactions observed in <10% of patients receiving the combination were pancreatitis, panniculitis, bradycardia, and rhabdomyolysis.

**Laboratory Abnormalities.** In the COMBI-d and COMBI-v studies, treatment-emergent laboratory abnormalities occurring in ≥10% of patients receiving the combination were hyperglycemia (60%), increased AST (59%), increased blood alkaline phosphatase (49%), increased ALT (48%), hypoalbuminemia (48%), neutropenia (46%), anemia (43%), hypophosphatemia (38%), lymphopenia (32%), hypokalemia (25%), and thrombocytopenia (21%).