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.

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.
Introduction

As a health care provider, you play an essential role in helping patients manage their treatment with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib). This guide provides information about the most serious and most common adverse drug reactions that may occur when taking TAFINLAR + MEKINIST. While adverse reactions are not always manageable, this guide provides important information about some recommended management strategies for certain adverse reactions, including how to:

- Monitor patients for adverse reactions
- Counsel patients on the role they can take in managing side effects
- Manage certain adverse reactions based on your clinical judgment and the information provided throughout this guide

Note: The safety and efficacy of TAFINLAR + MEKINIST were evaluated in two phase 3 trials, COMBI-d and COMBI-v. Where appropriate, pooled safety data from COMBI-d and COMBI-v have been used.

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- Summary of Warnings and Precautions
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  - Tumor Promotion in BRAF Wild-Type Melanoma
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  - Venous Thromboembolism
  - Cardiomyopathy
  - Ocular Toxicities
  - Interstitial Lung Disease
  - Serious Febrile Drug Reactions
  - Serious Skin Toxicity
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  - Glucose-6-Phosphate Dehydrogenase Deficiency
  - Embryo-Fetal Toxicity
- Adverse Reactions in COMBI-d and COMBI-v
- Additional Resources

This guide does not provide medical advice. Always use your clinical judgment when prescribing TAFINLAR + MEKINIST, and when monitoring and managing adverse reactions to treatment. You are encouraged to report side effects to Novartis and the FDA.

Contact Novartis: 1-888-669-6682
Contact the FDA: 1-800-FDA-1088
www.fda.gov/medwatch

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.
Dosing and Administration

DOSING

Recommended dose: TAFINLAR® (dabrafenib) 150 mg twice daily + MEKINIST® (trametinib) 2 mg once daily

Morning

TAFINLAR 150 mg
(2 x 75 mg)

Evening

TAFINLAR 150 mg
(2 x 75 mg)

Take MEKINIST at the same time each day with either the morning dose OR evening dose of TAFINLAR

Both TAFINLAR and MEKINIST should be taken without food, at least 1 hour before or 2 hours after a meal

12-hour interval between TAFINLAR doses

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.

TAFINLAR

- Do not take a missed dose of TAFINLAR within 6 hours of the next dose of TAFINLAR
- Do not open, crush, or break TAFINLAR capsules

MEKINIST

- Do not take a missed dose of MEKINIST within 12 hours of the next dose of MEKINIST

PATIENT SELECTION

- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with MEKINIST
- Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at https://www.fda.gov/CompanionDiagnostics
- TAFINLAR + MEKINIST is not indicated for the treatment of patients with wild-type BRAF melanoma

DOSE FORMS AND STRENGTHS

Capsules and tablets shown are not actual size.

TAFINLAR

- 75 mg capsule
- 50 mg capsule

MEKINIST

- 2 mg tablet
- 0.5 mg tablet

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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.
Dosing and Administration (continued)

**STORAGE AND HANDLING**
- **TAFINLAR®** (dabrafenib): Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
- **MEKINIST®** (trametinib): Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes

**DRUG INTERACTIONS**
- Avoid concurrent administration of strong inhibitors of CYP3A4 or CYP2C8
- Avoid concurrent administration of strong inducers of CYP3A4 or CYP2C8
- Concomitant use with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 may result in loss of efficacy of these agents

**DOSE MODIFICATIONS**
The overall management of certain adverse reactions requires treatment interruption, dose reduction, or treatment discontinuation, depending on severity (see tables on page 5).

**DOSE REDUCTIONS FOR TAFINLAR AND MEKINIST**

<table>
<thead>
<tr>
<th>TAFINLAR starting dose</th>
<th>150 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st dose reduction</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>2nd dose reduction</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>3rd dose reduction</td>
<td>50 mg twice daily</td>
</tr>
<tr>
<td>Subsequent modification</td>
<td>Permanently discontinue TAFINLAR if unable to tolerate 50 mg orally twice daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MEKINIST starting dose</th>
<th>2 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st dose reduction</td>
<td>1.5 mg once daily</td>
</tr>
<tr>
<td>2nd dose reduction</td>
<td>1 mg once daily</td>
</tr>
<tr>
<td>Subsequent modification</td>
<td>Permanently discontinue MEKINIST if unable to tolerate 1 mg orally once daily</td>
</tr>
</tbody>
</table>

**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.

**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.

Advise 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 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.

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.
**Recommended Dose Modifications**

### Febrile Drug Reaction
- Fever of 101.3°F-104°F
- Fever complicated by rigors, hypotension, dehydration, or renal failure

- Withhold TAFINLAR until fever resolves. Then resume at same or lower dose level.
- Withhold MEKINIST until fever resolves. Then resume MEKINIST at same or lower dose level.
- Or
- Permanently discontinue TAFINLAR.
- Or
- Permanently discontinue MEKINIST.

### Cutaneous Drug Reaction
- Intolerable grade 2 skin toxicity
- Grade 3 or 4 skin toxicity

- Withhold TAFINLAR 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 is below institutional lower limits of normal (LLN) from pretreatment value
- Symptomatic congestive heart failure
- Absolute decrease in LVEF of >20% from baseline that is below LLN

- Withhold TAFINLAR, if improved, then resume at the same dose.
- Withhold MEKINIST until fever resolves. Then resume MEKINIST at same or lower dose level.
- Or
- Permanently discontinue TAFINLAR.
- Or
- Permanently discontinue MEKINIST.

### Venous Thromboembolism
- Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)
- Life-threatening PE

- Do not modify the dose of TAFINLAR.
- Withhold MEKINIST until fever resolves. Then resume MEKINIST at same or lower dose level.
- Or
- Permanently discontinue TAFINLAR.
- Or
- Permanently discontinue MEKINIST.

### Ocular Toxicities
- Retinal pigment epithelial detachments (RPED)
- Uveitis including iritis and iridocyclitis that is mild or moderate but does not respond to ocular therapy
- Severe uveitis

- Withhold TAFINLAR for up to 6 weeks.
- If improved to grade 0-1, resume at the same dose level.
- If not improved, permanently discontinue TAFINLAR.

### Pulmonary Drug Reaction
- Interstitial lung disease/pneumonitis

- Withhold TAFINLAR for up to 3 weeks.
- If improved, resume at same or lower dose level.
- If not improved, permanently discontinue TAFINLAR.

### Other
- Intolerable grade 2 adverse reactions
- Any grade 3 adverse reaction
- First occurrence of any grade 4 adverse reaction
- Recurrent grade 4 adverse reaction

- Withhold MEKINIST for up to 3 weeks.
- Do not modify the dose of TAFINLAR.
- Or
- Permanently discontinue MEKINIST.

### Severity of Adverse Reaction

- **Febrile Drug Reaction**
- **Cutaneous Drug Reaction**
- **Cardiac Drug Reaction**
- **Venous Thromboembolism**

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1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
2. See page 4 for recommended dose reductions of TAFINLAR and MEKINIST when administered in combination.
3. Refer to the full Prescribing Information for TAFINLAR or the full Prescribing Information for MEKINIST.

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*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.
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® (dabrafenib) 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® (trametinib) 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. Urgently (within 24 hours) perform ophthalmic 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.
New Primary Malignancies

OVERVIEW

New primary malignancies, cutaneous and noncutaneous, can occur with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib).

Cutaneous malignancies observed with TAFINLAR + MEKINIST

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>TAFINLAR + MEKINIST</th>
<th>TAFINLAR plus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td>3.3%</td>
<td>6%</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinomas</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>keratoacanthoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New primary melanoma</td>
<td>0.5%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

- Median time to first diagnosis of basal cell carcinoma was 5.1 months (range: 2.8 to 23.9 months) in patients receiving TAFINLAR + MEKINIST and 4.4 months (range: 29 days to 16.5 months) in patients receiving TAFINLAR plus placebo.
- Among the 7 patients receiving TAFINLAR + MEKINIST who developed basal cell carcinoma, 2 (29%) experienced more than one occurrence (range: 1 to 3).
- Median time to first diagnosis of cuSCC was 7.3 months (range: 1.8 to 16.8 months) in patients receiving TAFINLAR + MEKINIST and 2 months (range: 9 days to 20.9 months) in patients receiving TAFINLAR plus placebo.

DOSE MODIFICATIONS

- No dose modifications are required in patients who develop new primary cutaneous malignancies.

MONITORING

- Perform dermatologic evaluations prior to initiation of TAFINLAR + MEKINIST, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR + MEKINIST.

IMPORANT SAFETY INFORMATION (CONTINUED)

Perform ophthalmic 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 ophthalmic evaluation within 3 weeks, resume MEKINIST. Reduce the dose or discontinue MEKINIST if no improvement after 3 weeks.

Noncutaneous malignancies observed with TAFINLAR + MEKINIST

- Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms.

DOSE MODIFICATIONS

- Monitor patients receiving TAFINLAR + MEKINIST for signs or symptoms of noncutaneous malignancies.

PATIENT COUNSELING FOR NEW PRIMARY MALIGNANCIES

- Advise patients to contact their health care provider immediately about any new symptoms that develop during treatment with TAFINLAR + MEKINIST, including skin changes such as:
  - any new lesions
  - changes to existing lesions on their skin
  - signs and symptoms of other malignancies
  - new wart
  - skin sore or reddish bump that bleeds or does not heal
  - change in size or color of a mole

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.
OVERVIEW

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 initiating TAFINLAR® (dabrafenib) + MEKINIST® (trametinib)

Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur.

Hemorrhagic events

<table>
<thead>
<tr>
<th>Hemorrhagic events</th>
<th>TAFINLAR + MEKINIST (n=209)</th>
<th>TAFINLAR plus placebo (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic events</td>
<td>19%</td>
<td>15%</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- 1.4% (3/209) of patients receiving TAFINLAR + MEKINIST developed fatal intracranial hemorrhage compared with none of the patients receiving TAFINLAR plus placebo

PATIENT COUNSELING

- Advise patients to tell their health care provider and get medical help right away if they have any signs of bleeding, including:
  - headaches, dizziness, or feeling weak
  - coughing up blood or blood clots
  - vomiting blood or vomit that looks like “coffee grounds”
  - red or black stool that looks like tar

DOSE MODIFICATIONS

- Hemorrhagic events
  - 15%
  - Gastrointestinal hemorrhage
  - 6%

TAFINLAR®:

- If improved to grade 0-1, resume at a lower dose level
- If not improved, permanently discontinue

MEKINIST®:

- If improved to grade 0-1, resume at a lower dose level
- If not improved, permanently discontinue

Grade 3 hemorrhagic events

- Persistent grade 3 or any grade 4 hemorrhagic events

- Permanently discontinue TAFINLAR

- Permanently discontinue MEKINIST

Severe Adverse Reaction

- National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- See page 4 for recommended dose reductions of TAFINLAR and MEKINIST when administered in combination.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Uveitis:

Uveitis (including iritis and iridocyclitis) occurred in 1% of 586 patients across multiple clinical trials treated with TAFINLAR as a single agent, and uveitis (including iridocyclitis) in 2% of 559 patients treated with the combination. Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops.

Monitor patients for visual signs and symptoms of uveitis (eg, change in vision, photophobia, and eye pain). If iritis is diagnosed, administer ocular 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.

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.
Colitis and Gastrointestinal Perforation

OVERVIEW
Colitis and gastrointestinal perforation, including fatal outcomes, can occur with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib).

Colitis and gastrointestinal perforation

- Across clinical trials (MEKINIST [N=329], TAFINLAR + MEKINIST [N=559]), colitis occurred in 0.6% of patients and gastrointestinal perforation occurred in 0.3% of patients, respectively.

PATIENT COUNSELING
Advise patients to get medical help right away if they have any of the following symptoms:

- diarrhea
- stomach or abdominal pain
- fever
- nausea

IMPORTANT SAFETY INFORMATION (CONTINUED)
Interstitial Lung Disease (ILD). In clinical trials of MEKINIST (N=329), TAFINLAR + MEKINIST (N=559), 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.

Venous Thromboembolism

OVERVIEW
Venous thromboembolism can occur with TAFINLAR + MEKINIST.

Venous thromboembolism

Deep venous thrombosis (DVT) and pulmonary embolism (PE)

TAFINLAR + MEKINIST
(n=209)

2.8%

TAFINLAR plus placebo
(n=211)

0.9%

PATIENT COUNSELING
Advise patients to get medical help right away if they have any of the following symptoms:

- chest pain
- sudden shortness of breath or trouble breathing
- pain in legs with or without swelling
- swelling in arms or legs
- a cool pale arm or leg

DOSE MODIFICATIONS

Severity of Adverse Reaction

Uncomplicated DVT or PE

Do not modify the dose of TAFINLAR.

Life-threatening PE

Permanently discontinue TAFINLAR.

Permanently discontinue MEKINIST.

Deep venous thrombosis (DVT) and pulmonary embolism (PE) with TAFINLAR + MEKINIST versus TAFINLAR plus placebo

Severity of Adverse Reaction

TAFINLAR

MEKINIST

Uncomplicated DVT or PE

Do not modify the dose of TAFINLAR.

Permanently discontinue TAFINLAR.

Permanently discontinue MEKINIST.

Life-threatening PE

0.9%

2.8%

6.1%

IMPORTANT SAFETY INFORMATION (CONTINUED)
Venous thromboembolism

Venous thromboembolism

Uncomplicated DVT or PE

Life-threatening PE

- Uncomplicated DVT or PE
- Life-threatening PE

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

Do not modify the dose of TAFINLAR.

Permanently discontinue MEKINIST.

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

*See page 4 for recommended dose reductions of TAFINLAR and MEKINIST when administered in combination.

IMPORTANT SAFETY INFORMATION (CONTINUED)
Serious Febrile Drug Reactions. The incidence and severity of pyrexia are increased when the combination is used compared with TAFINLAR as a single agent.

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.
Cardiomyopathy

OVERVIEW
Cardiomyopathy, including cardiac failure, can occur with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib). Cardiomyopathy

- Median time to onset of cardiomyopathy was 8.2 months (range: 28 days to 24.9 months) in patients receiving TAFINLAR + MEKINIST and 4.4 months (range: 28 days-19.1 months) in patients receiving TAFINLAR plus placebo.
- Cardiomyopathy was identified within the first month in 2 of 12 patients and 2 of 6 patients receiving TAFINLAR + MEKINIST and TAFINLAR plus placebo, respectively.
- Cardiomyopathy resulted in dose interruption of TAFINLAR in 4.4% of patients receiving TAFINLAR + MEKINIST and 2.4% of patients receiving TAFINLAR plus placebo. Dose reductions occurred in 0.5% of patients receiving TAFINLAR plus placebo. TAFINLAR was permanently discontinued in 1% of patients receiving TAFINLAR + MEKINIST and TAFINLAR plus placebo.
- Cardiomyopathy resolved in 10 of 12 patients receiving TAFINLAR + MEKINIST and 3 of 6 patients receiving TAFINLAR plus placebo.

MONITORING
- Assess LVEF by an echocardiogram or a multigated acquisition (MUGA) scan before initiation of therapy, 1 month after initiation, and then at 2- to 3-month intervals while on treatment.

DOSE MODIFICATIONS

<table>
<thead>
<tr>
<th>Severity of Adverse Reaction</th>
<th>TAFINLAR®</th>
<th>MEKINIST®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, absolute decrease in LVEF of ≥10% from baseline and is below institutional LLN from pretreatment value</td>
<td>Do not modify the dose of TAFINLAR.</td>
<td>Withhold MEKINIST for up to 4 weeks.</td>
</tr>
<tr>
<td>Symptomatic congestive heart failure</td>
<td>Withhold TAFINLAR if improved, then resume at the same dose.</td>
<td>If improved to normal LVEF value, resume at a lower dose level.</td>
</tr>
<tr>
<td>Absolute decrease in LVEF of &gt;20% from baseline that is below LLN</td>
<td>Permanently discontinue TAFINLAR.</td>
<td>If not improved to normal LVEF value, permanently discontinue.</td>
</tr>
</tbody>
</table>

Cardiac drug reaction

TAFINLAR + MEKINIST (n=206) 6%
TAFINLAR plus placebo (n=207) 2.9%

IMPORTANT SAFETY INFORMATION (CONTINUED)
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/rigors in 0.4%, dehydration in 1.8%, renal failure in 0.5%, and syncope in 0.7% of 559 patients receiving the combination.

PATIENT COUNSELING
Advise patients to tell their health care provider right away if they have any of the following signs and symptoms of a heart problem:
- feels like heart is pounding or racing
- shortness of breath
- swelling of ankles and feet
- feels lightheaded

IMPORTANT SAFETY INFORMATION (CONTINUED)
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.

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.
OVERVIEW

Ocular toxicities such as retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), and uveitis (including iritis and iridocyclitis), can occur with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib).

Retinal Vein Occlusion

Across all clinical trials with MEKINIST, the incidence of RVO was 0.2% (4/1,749). RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Retinal Pigment Epithelial Detachment

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.

Uveitis

Uveitis (including iritis and iridocyclitis) occurred in 2% of 559 patients treated with TAFINLAR + MEKINIST in COMBI-d and COMBI-v. Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops.

PATIENT COUNSELING

Advise patients to tell their health care provider right away if they have any of the following symptoms of eye problems:

- blurred vision, loss of vision, or other vision changes
- see color dots
- halo (seeing blurred outline around objects)
- eye pain, swelling, or redness

DOSE MODIFICATIONS

Severity of Adverse Reaction* | TAFINLAR® | MEKINIST®
---|---|---
Retinal pigment epithelial detachments | Do not modify the dose of TAFINLAR. | Withhold MEKINIST for up to 3 weeks.
Retinal vein occlusion | Do not modify the dose of TAFINLAR. | Withhold TAFINLAR for up to 6 weeks.
Uveitis (including iritis and iridocyclitis) that is mild or moderate but does not respond to ocular therapy | Permanently discontinue MEKINIST. | If improved to grade 0-1, then resume at the same or lower dose level.
Severe uveitis | Permanently discontinue MEKINIST. | If not improved, permanently discontinue MEKINIST.

Ocular toxicities

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Withhold TAFINLAR for fever of 101.3ºF or higher. Withhold MEKINIST for fever higher than 104ºF. Withhold TAFINLAR and MEKINIST for any serious febrile reaction or fever complicated by hypotension, rigor or chills, dehydration, or renal failure, and evaluate for signs and symptoms of infection. 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.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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.
Interstitial Lung Disease

**OVERVIEW**

Interstitial lung disease can occur.

**Interstitial lung disease**

<table>
<thead>
<tr>
<th>Condition</th>
<th>TAFINLAR + MEKINIST</th>
<th>TAFINLAR + placeo</th>
<th>MEKINIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial lung disease or pneumonitis</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**PATIENT COUNSELING**

Advise patients to tell their health care provider right away if they have new or worsening symptoms of lung or breathing problems, including:

- dyspnea (shortness of breath)
- cough

**IMPORTANT SAFETY INFORMATION (CONTINUED)**

**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.

**DOSE MODIFICATIONS**

Severity of Adverse Reaction:
- Pulmonary drug reaction
  - Interstitial lung disease/pneumonitis
  - Do not modify the dose of TAFINLAR.

TAFINLAR®:
- MeKINIST®:
  - Permanently discontinue.

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
*See page 4 for recommended dose reductions of TAFINLAR and MEKINIST when administered in combination.

**IMPORTANT SAFETY INFORMATION (CONTINUED)**

**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.

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.
**Serious Febrile Drug Reactions (Pyrexia)**

**OVERVIEW**

Serious febrile drug reactions and fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure, can occur with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib). Pyrexia was the most common adverse reaction observed with TAFINLAR + MEKINIST.

**Pyrexia in COMBI-d and COMBI-v**

<table>
<thead>
<tr>
<th>All Grades</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAFINLAR: Arm of COMBI-d (n=211)</td>
<td>33%</td>
</tr>
<tr>
<td>Vemurafenib: Arm of COMBI-v (n=249)</td>
<td>21%</td>
</tr>
</tbody>
</table>

Grades per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care (activities of daily living)
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death related to AE

Of patients who experienced pyrexia:

- Grade 4 pyrexia was not observed with TAFINLAR + MEKINIST (n=0/559)

**PATIENT COUNSELING**

- Inform patients that fever is common during treatment with TAFINLAR + MEKINIST, but may also be serious. When taking TAFINLAR + MEKINIST, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever
- Advise patients to tell their health care provider right away if they get a fever during treatment with TAFINLAR + MEKINIST

**DOSE MODIFICATIONS**

- **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
  - Or
  - Permanently discontinue TAFINLAR
- **Fever complicated by rigors, hypotension, dehydration, or renal failure**
  - Withhold TAFINLAR until fever resolves. Then resume at same or lower dose level
- **Do not modify the dose of MEKINIST.**
  - Withhold MEKINIST until fever resolves. Then resume MEKINIST at same or lower dose level.

**IMPORTANT SAFETY INFORMATION (CONTINUED)**

Monitor serum glucose levels upon initiation, and as clinically appropriate in patients with preexisting diabetes or hyperglycemia.

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.
Serious Skin Toxicity

OVERVIEW

Serious skin toxicity can occur with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib).

SERIOUS SKIN TOXICITY IN COMBI-d AND COMBI-v

- In COMBI-d, the overall incidence of any skin toxicity was 55% for patients receiving TAFINLAR + MEKINIST compared with 55% for patients receiving TAFINLAR plus placebo.
- No serious or severe cases of skin toxicity occurred in patients treated with TAFINLAR + MEKINIST.
- The median time to initial onset of skin toxicity in patients treated with TAFINLAR + MEKINIST was 1.9 months (range: 1 day-22.1 months); median time to resolution of skin toxicity was 1.2 months (range: 1 day-24.4 months).
- Reductions in the dose of MEKINIST were required in 5% of patients receiving TAFINLAR + MEKINIST.
- No patients required permanent discontinuation of TAFINLAR or MEKINIST for skin toxicity.

PATIENT COUNSELING

Advise patients to tell their health care provider if they get any of the following symptoms:
- skin rash that is bothersome, gets worse, or does not go away
- acne
- redness, swelling, peeling, or tenderness of hands or feet
- skin redness

DOSE MODIFICATIONS

Severity of Adverse Reaction
- Intolerable grade 2 skin toxicity
- Grade 3 or 4 skin toxicity

Withhold TAFINLAR for up to 3 weeks.
- If improved, resume at a lower dose level
- If not improved, permanently discontinue

Withhold MEKINIST for up to 3 weeks.
- If improved, resume at a lower dose level
- If not improved, permanently discontinue

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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.
**OVERVIEW**

Hyperglycemia requiring an increase in the dose of, or initiation of, insulin or oral hypoglycemic agent therapy can occur with TAFINLAR® (dabrafenib) + MEKINIST® (trametinib).

**Hyperglycemia**

- In COMBI-d, 27% (4/15) of patients with a history of diabetes receiving the combination and 13% (2/16) of patients with a history of diabetes receiving single-agent TAFINLAR required more intensive hypoglycemic therapy.

**MONITORING**

Monitor serum glucose levels upon initiation and as clinically appropriate when TAFINLAR + MEKINIST is administered in patients with preexisting diabetes or hyperglycemia.

**PATIENT COUNSELING**

Advise patients to tell their health care provider if they have any of the following symptoms of severe high blood sugar:

- increased thirst
- urinating more often than normal, or urinating an increased amount of urine

**DOSE MODIFICATIONS**

<table>
<thead>
<tr>
<th>Severity of Adverse Reaction*</th>
<th>TAFINLAR®</th>
<th>MEKINIST®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intolerable grade 2 adverse reactions</td>
<td>Withhold TAFINLAR.</td>
<td>Withhold MEKINIST.</td>
</tr>
<tr>
<td>Any grade 3 adverse reaction</td>
<td>If improved to grade 0-1, resume at a lower dose level</td>
<td>If improved to grade 0-1, resume at a lower dose level</td>
</tr>
<tr>
<td>First occurrence of any grade 4 adverse reaction</td>
<td>Withhold TAFINLAR until adverse reaction improves to grade 0-1. Then resume at a lower dose level.</td>
<td>Withhold MEKINIST until adverse reaction improves to grade 0-1. Then resume at a lower dose level.</td>
</tr>
<tr>
<td>Recurrent grade 4 adverse reaction</td>
<td>Permanently discontinue TAFINLAR.</td>
<td>Permanently discontinue MEKINIST.</td>
</tr>
</tbody>
</table>

**Common Terminology Criteria for Adverse Events, version 4.0: Hyperglycemia**

- Grade 1: >ULN – 160 mg/dL (>ULN – 8.9 mmol/L)
- Grade 2: >160 – 250 mg/dL (>8.9 – 13.9 mmol/L)
- Grade 3: >250 – 500 mg/dL (>13.9 – 27.8 mmol/L); hospitalization indicated
- Grade 4: >500 mg/dL (>27.8 mmol/L); life-threatening consequences

*National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
*See page 4 for recommended dose reductions of TAFINLAR and MEKINIST when administered in combination.

**IMPORTANT SAFETY INFORMATION (CONTINUED)**

**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%).

**IMPORTANT SAFETY INFORMATION (CONTINUED)**

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.

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.
**Glucose-6-Phosphate Dehydrogenase Deficiency**

**OVERVIEW**
TAFINLAR® (dabrafenib), which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

**MONITORING**
Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR + MEKINIST® (trametinib).

**PATIENT COUNSELING**
Advise patients to tell their health care provider if they have any of the following signs or symptoms:
- yellow skin (jaundice)
- weakness or dizziness
- shortness of breath

**Embryo-Fetal Toxicity**

**OVERVIEW**
TAFINLAR + MEKINIST can both cause fetal harm when administered to a pregnant woman.

**PATIENT COUNSELING**
- 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 tell their health care provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR + MEKINIST

**IMPORTANT SAFETY INFORMATION (CONTINUED)**
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%), hyponatremia (25%), and thrombocytopenia (21%).
### Discontinuations Due to Adverse Reactions

#### Adverse Reactions in COMBI-d and COMBI-v

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TAFINLAR (n=211)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>64</td>
<td>19</td>
</tr>
<tr>
<td>Chills</td>
<td>21</td>
<td>0.5</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Vemurafenib (n=349)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>33</td>
<td>1.9</td>
</tr>
<tr>
<td>Chills</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>Edema</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>TAFINLAR + MEKINIST (Arm of COMBI-d, n=559)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>0.6</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vemurafenib + trametinib (Arm of COMBI-v, n=559)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36</td>
<td>0.6</td>
</tr>
<tr>
<td>Chills</td>
<td>38</td>
<td>0.3</td>
</tr>
<tr>
<td>Edema</td>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>TAFINLAR (Arm of COMBI-d, n=211)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
<td>1.4</td>
</tr>
<tr>
<td>Chills</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vemurafenib (Arm of COMBI-v, n=349)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
<td>0.6</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Adverse Reactions in COMBI-d LEADING TO DOSE MODIFICATIONS OF TAFINLAR

- Most common adverse reaction resulting in permanent discontinuation of TAFINLAR was pyrexia (1.9%)
- Adverse reactions leading to dose reductions of TAFINLAR occurred in 26% of patients
  - Most commonly cited reasons for dose reductions were pyrexia (14%), neutropenia (1.9%), rash (1.9%), and chills (1.9%)
- Adverse reactions leading to dose interruptions of TAFINLAR occurred in 56% of patients
  - Most commonly cited reasons for dose interruptions were pyrexia (35%), chills (11%), vomiting (7%), nausea (5%), and decreased ejection fraction (5%)

#### Adverse Reactions in COMBI-v LEADING TO DOSE MODIFICATIONS OF MEKINIST

- Most common adverse reaction resulting in permanent discontinuation of MEKINIST was pyrexia (1.9%) and decreased ejection fraction (1.4%)
- Adverse reactions leading to dose reductions of MEKINIST occurred in 18% of patients
  - Most commonly cited reasons for dose reductions were pyrexia (2.9%), neutropenia (1.9%), decreased ejection fraction (1.9%), and rash (1.9%)
- Adverse reactions leading to dose interruptions of MEKINIST occurred in 46% of patients
  - Most commonly cited reasons for dose interruptions were pyrexia (18%), chills (7%), vomiting (6%), and decreased ejection fraction (4.8%)

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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

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® (dabrafenib) in combination with MEKINIST® (trametinib) was 3.3% (7/209) vs 6.5% (13/211); cutaneous squamous cell carcinoma (cSCC), including keratoacanthoma 3% vs 7%, and nonmelanoma skin cancer 0.9% (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 cSCC was 7.3 months (range: 1.8-16.8 months) in patients receiving the combination and 2 months (range: 9-20.9 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 receive new primary cutaneous malignancies.

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 with new primary 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. Cardiomyopathy occurred in 10 of 12 patients receiving the combination and in 3 of 6 patients receiving TAFINLAR as a single agent. Cardiomyopathy resolved in 10 of 12 patients receiving TAFINLAR as a single agent. Asystole was treated 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 <50%. For symptomatic cardiomyopathy or persistent asymptomatic LV dysfunction of ≥20% from baseline that is below LNN that does not resolve within 4 weeks, permanently discontinue TAFINLAR and withhold MEKINIST. Cardiomyopathy resolved in 10 of 12 patients receiving the combination vs 0.9% of 211 patients treated with TAFINLAR as a single agent.

Permanently discontinue TAFINLAR for patients who developed noncutaneous malignancies. Permanently discontinue TAFINLAR for RAS-mutation-positive noncutaneous malignancies. Cardiomyopathy occurred in 10 of 12 patients receiving the combination and in 3 of 6 patients receiving TAFINLAR as a single agent. Cardiomyopathy resolved in 10 of 12 patients receiving TAFINLAR as a single agent. Permanently discontinue TAFINLAR for persistent grade 2 or greater uveitis of ≥6 weeks duration.

Intestinal Lymph Vascular 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 5.4% (10/189) vs 0.2% (4/1749) and was associated with severe chills/rigors in 0.4%, dehydration in 1.8%, renal failure, or syndrome occurred in 17% (39/235). Fever was complicated by severe chills/rigors in 0.4%, dehydration in 1.8%, renal failure in 0.5%, and syndrome in 0.7% of 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.

Please see additional Important Safety Information for TAFINLAR and MEKINIST on the following page.
TAFINLAR® (dabrafenib) and MEKINIST® (trametinib) for fever of 101.3°F or higher. Withhold MEKINIST® (trametinib) for fever higher than 104°F. Withhold TAFINLAR and MEKINIST for any serious 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. 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. Withhold TAFINLAR and MEKINIST for any serious or severe febrile reaction or fever associated with complications. 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. 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. 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 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 grade 3 or 4 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 hemoglobin (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, paronychia, bradycardia, and rhabdomyolysis. Laboratory Abnormalities. In the COMBI-d and COMBI-v studies, treatment-emergent laboratory abnormalities occurring in ≥20% of patients receiving the combination were hyperbilirubinemia (60%), increased AST (59%), increased blood alkaline phosphatase (49%), increased ALT (48%), hypoalbuminemia (48%), neutropenia (46%), anemia (43%), hypophosphatemia (38%), lymphopenia (32%), hypoaalbuminemia (25%), and thrombocytopenia (21%). References: 1. Supplement to: Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:1030-39. 2. Data on file. Clinical study report MEK115306. Novartis Pharmaceuticals Corp; July 3, 2014. 3. Data on file. Clinical study report MEK163513. Novartis Pharmaceuticals Corp; January 15, 2015.