HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAFINLAR safely and effectively. See full prescribing information for TAFINLAR.

TAFINLAR® (dabrafenib) capsules, for oral use
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage (1.3, 1.4)	6/2017
Dosage and Administration (2.1)	6/2017
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.8)	6/2017

INDICATIONS AND USAGE

TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1.1)

TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with:

- unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.2)
- metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test. (1.3)

Limitation of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF NSCLC. (1.4, 5.2)

DOSAGE AND ADMINISTRATION

- Melanoma: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent. (2.1) Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib. (2.1)
- NSCLC: Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib. (2.1)
- The recommended dose of TAFINLAR is 150 mg orally twice daily. Take TAFINLAR at least 1 hour before or at least 2 hours after a meal. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg, 75 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- New primary malignancies, cutaneous and non-cutaneous: Can occur when TAFINLAR is administered as a single agent or with trametinib. Monitor patients for new malignancies prior to, or while on therapy, and following discontinuation of treatment. (5.1, 2.3)
- Tumor promotion in BRAF wild-type tumors: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Hemorrhage: Major hemorrhagic events can occur in patients receiving TAFINLAR with trametinib. Monitor for signs and symptoms of bleeding. (5.3, 2.3)
- Cardiomyopathy: Assess LVEF before treatment with TAFINLAR and trametinib, after one month of treatment, then every 2 to 3 months thereafter. (5.4, 2.3)
- Uveitis: Perform ophthalmologic evaluation for any visual disturbances. (5.5, 2.3)
- Serious febrile reactions: Incidence and severity of pyrexia are increased with TAFINLAR and trametinib. (5.6, 2.3)
- Serious skin toxicity: Monitor for skin toxicities. Discontinue for intolerable Grade 2 or for Grade 3 or 4 rash not improving within 3 weeks despite interruption of TAFINLAR. (5.7, 2.3)
- Hyperglycemia: Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia. (5.8)
- Glucose-6-phosphate dehydrogenase deficiency: Closely monitor for hemolytic anemia. (5.9)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use an effective non-hormonal method of contraception. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (≥20%) for TAFINLAR as a single agent are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. (6.1)
Most common adverse reactions (≥20%) for TAFINLAR, in combination with trametinib, include:

- Melanoma: pyrexia, rash, chills, headache, arthralgia, and cough. (6.1)
- NSCLC: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid concurrent administration of strong inhibitors of CYP3A4 or CYP2C8. (7.1)
- Concomitant use with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 may result in loss of efficacy of these agents. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed. (8.2)
- Females and Males of Reproductive Potential: May impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma

TAFINLAR® is indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

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

1.3 BRAF V600E Mutation-Positive Metastatic NSCLC

TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.

1.4 Limitation of Use

TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF NSCLC *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Melanoma

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent *[see Warnings and Precautions (5.2) and Clinical Studies (14.1)]*. Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib *[see Warnings and Precautions (5.2) and Clinical Studies (14.1)]*. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

NSCLC

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR and trametinib *[see Clinical Studies (14.2)]*. Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosing

The recommended dosage regimen of TAFINLAR is 150 mg orally taken twice daily, approximately 12 hours apart as a single agent or with trametinib. Continue treatment until disease progression or unacceptable toxicity occurs.

Take TAFINLAR at least 1 hour before or 2 hours after a meal *[see Clinical Pharmacology (12.3)]*. 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.

2.3 Dose Modifications

Review the Full Prescribing Information for trametinib for recommended dose modifications. Dose modifications are not recommended for TAFINLAR when administered with trametinib for the following adverse reactions of trametinib: retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), interstitial lung disease/pneumonitis, and uncomplicated venous thromboembolism.

For New Primary Cutaneous Malignancies

No dose modifications are required.

For New Primary Non-Cutaneous Malignancies

Permanently discontinue TAFINLAR in patients who develop RAS mutation-positive non-cutaneous malignancies.

Table 1. Recommended Dose Reductions

Dose Reductions for TAFINLAR	
First Dose Reduction	100 mg orally twice daily
Second Dose Reduction	75 mg orally twice daily
Third Dose Reduction	50 mg orally twice daily
Subsequent Modification	Permanently discontinue TAFINLAR if unable to tolerate 50 mg orally twice daily

Table 2. Recommended Dose Modifications for TAFINLAR

Severity of Adverse Reaction[a]	**TAFINLAR[b]**
Febrile Drug Reaction	
• Fever of 101.3°F to 104°F	Withhold TAFINLAR until fever resolves. Then resume at same or lower dose level.
• Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure	• Withhold TAFINLAR until fever resolves. Then resume at a lower dose level. Or • Permanently discontinue TAFINLAR.
Cutaneous	
• 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.
Cardiac	
• Symptomatic congestive heart failure • Absolute decrease in LVEF of greater than 20% from baseline that is below LLN	Withhold TAFINLAR, if improved, then resume at the same dose.
Uveitis	
• Uveitis including iritis and iridocyclitis	If mild or moderate uveitis does not respond to ocular 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.

Severity of Adverse Reaction[a]	TAFINLAR[b]
Other	
• Intolerable Grade 2 adverse reactions • Any Grade 3 adverse reaction	Withhold TAFINLAR. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
• First occurrence of any Grade 4 adverse reaction	• Withhold TAFINLAR until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue TAFINLAR.
• Recurrent Grade 4 adverse reaction	Permanently discontinue TAFINLAR.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.
[b] See Table 1 for recommended dose reductions of TAFINLAR.

3 DOSAGE FORMS AND STRENGTHS

50 mg capsules: Dark red capsule imprinted with 'GS TEW' and '50 mg'.

75 mg capsules: Dark pink capsule imprinted with 'GS LHF' and '75 mg'.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

Review the Full Prescribing Information for trametinib for information on the serious risks of trametinib prior to initiation of TAFINLAR in combination with trametinib.

5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, can occur when TAFINLAR is administered as a single agent or when used with trametinib.

Cutaneous Malignancies

TAFINLAR results in an increased incidence of cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma.

In the BREAK-3 study in patients with melanoma, cutaneous squamous cell carcinomas and keratoacanthomas (cuSCC) occurred in 7% (14/187) of patients receiving TAFINLAR and in none of the patients receiving dacarbazine.

Across clinical trials of TAFINLAR (N = 586), the incidence of cuSCC was 11%. The median time to first cuSCC was 2.1 months (range: 7 days to 12.2 months). Of those patients who developed new cuSCC, approximately 33% developed one or more cuSCC with continued administration of TAFINLAR. The median time between diagnosis of the first cuSCC and the second cuSCC was 6 weeks.

In the COMBI-d study in patients with melanoma, the incidence of basal cell carcinoma in patients receiving TAFINLAR in combination with trametinib was 3.3% (7/209) compared with 6% (13/211) of patients receiving single-agent TAFINLAR. The median time to first diagnosis of basal cell carcinoma was 5.1 months (range: 2.8 to 23.9 months) in the TAFINLAR plus trametinib arm and was 4.4 months (range: 29 days to 16.5 months) in the single-agent TAFINLAR arm. Among the 7 patients receiving TAFINLAR with trametinib who developed basal cell carcinoma, 2 (29%) experienced more than one occurrence (range: 1 to 3).

Cutaneous squamous cell carcinoma and keratoacanthoma occurred in 3% of patients receiving TAFINLAR with trametinib and 10% of patients receiving single-agent TAFINLAR. The median time to first diagnosis of cuSCC was 7.3 months (range: 1.8 to 16.8 months) in the TAFINLAR plus trametinib arm and 2 months (range: 9 days to 20.9 months) in the single-agent TAFINLAR arm.

New primary melanoma occurred in 0.5% (1/209) of patients receiving TAFINLAR with trametinib and in 1.9% (4/211) of patients receiving single-agent TAFINLAR.

In Study BRF113928 in patients with NSCLC, cuSCC occurred in 3.2% (3/93) of patients with NSCLC receiving TAFINLAR plus trametinib with a time to onset of the first occurrence of 25 days, 3.5 months, and 12.3 months.

Perform dermatologic evaluations prior to initiation of TAFINLAR, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR. No dose modifications of TAFINLAR are required in patients who develop new primary cutaneous malignancies *[see Dosage and Administration (2.3)]*.

Non-cutaneous Malignancies

Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. In the COMBI-d study, non-cutaneous malignancies occurred in 1.4% (3/209) of patients receiving TAFINLAR with trametinib and in 2.8% (6/211) of patients receiving single-agent TAFINLAR. In Study BRF113928, non-cutaneous malignancies occurred in 1.1% (1/93) of patients receiving TAFINLAR with trametinib.

Monitor patients receiving TAFINLAR for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies *[see Dosage and Administration (2.3)]*.

5.2 Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of TAFINLAR as a single agent or in combination with trametinib *[see Indications and Usage (1), Dosage and Administration (2.1)]*.

5.3 Hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur when TAFINLAR is administered with trametinib.

In the COMBI-d study, the incidence of hemorrhagic events in patients receiving TAFINLAR with trametinib was 19% (40/209) compared with 15% (32/211) of patients receiving single-agent TAFINLAR. Gastrointestinal hemorrhage occurred in 6% (12/209) of patients receiving TAFINLAR with trametinib compared with 3% (6/211) of patients receiving single-agent TAFINLAR. Intracranial hemorrhage was fatal in 1.4% (3/209) of patients receiving TAFINLAR with trametinib compared with none of the patients receiving single-agent TAFINLAR. In Study BRF113928, fatal hemorrhagic events occurred in 2.2% (2/93) of patients receiving TAFINLAR with trametinib; these events were retroperitoneal hemorrhage and subarachnoid hemorrhage.

Permanently discontinue TAFINLAR for all Grade 4 hemorrhagic events and for any persistent Grade 3 hemorrhagic events. Withhold TAFINLAR for Grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

5.4 Cardiomyopathy

Cardiomyopathy can occur with TAFINLAR.

In the COMBI-d study, all patients were required to have an echocardiogram at baseline to document normal left ventricular ejection fraction (LVEF) and serial echocardiograms at Week 4, Week 12, and every 12 weeks thereafter. In this study, cardiomyopathy, defined as a decrease in LVEF ≥10% from baseline and below the institutional lower limit of normal, occurred in 6% (12/206) of patients receiving TAFINLAR with trametinib

and 2.9% (6/207) of patients receiving single-agent TAFINLAR. The median time to onset of cardiomyopathy on the TAFINLAR plus trametinib arm was 8.2 months (range: 28 days to 24.9 months), and was 4.4 months (range: 28 days to 19.1 months) on the TAFINLAR arm.

In the COMBI-d study, cardiomyopathy was identified within the first month of initiation of TAFINLAR with trametinib in 2 of 12 patients, and in 2 of 6 patients receiving single-agent TAFINLAR. Development of cardiomyopathy in patients receiving TAFINLAR and trametinib resulted in dose interruption of TAFINLAR (4.4%) or discontinuation of TAFINLAR (1.0%). In patients receiving single-agent TAFINLAR, development of cardiomyopathy resulted in dose interruption (2.4%), dose reduction (0.5%), or discontinuation (1.0%). Cardiomyopathy resolved in 10 of 12 patients receiving TAFINLAR with trametinib, and in 3 of 6 patients receiving single-agent TAFINLAR.

In Study BRF113928, all patients were required to have an echocardiogram at baseline to document normal left ventricular ejection fraction (LVEF) and serial echocardiograms at Week 6, Week 15, and then every 9 weeks thereafter. Cardiomyopathy, defined as a decrease in LVEF below the institutional lower limit of normal with an absolute decrease in LVEF >10% below baseline, occurred in 9% (8/93) of patients receiving TAFINLAR with trametinib. The median time to onset of cardiomyopathy was 6.7 months (range: 1.4 months to 14.1 months). Cardiomyopathy in patients receiving TAFINLAR and trametinib resulted in dose interruption and permanent discontinuation of TAFINLAR in 3.2% and 2.2%, respectively. Cardiomyopathy resolved in 4 of 8 patients receiving TAFINLAR and trametinib.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of TAFINLAR with trametinib, one month after initiation of TAFINLAR, and then at 2- to 3-month intervals while on treatment. Withhold TAFINLAR for symptomatic cardiomyopathy or asymptomatic LV dysfunction of >20% from baseline that is below institutional lower limit of normal (LLN). Resume TAFINLAR at the same dose level upon recovery of cardiac function to at least the institutional LLN for LVEF and absolute decrease ≤10% compared to baseline *[see Dosage and Administration (2.3)]*.

5.5 Uveitis

Uveitis (including iritis and iridocyclitis) can occur with TAFINLAR.

Uveitis occurred in 1% (6/586) of patients receiving TAFINLAR across multiple clinical trials and in 2% (9/559) of patients receiving TAFINLAR with trametinib across randomized melanoma trials. Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops.

Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, 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 *[see Dosage and Administration (2.3)]*.

5.6 Serious Febrile Reactions

Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur with TAFINLAR.

The incidence and severity of pyrexia are increased when TAFINLAR is administered with trametinib compared with TAFINLAR as a single agent *[see Adverse Reactions (6.1)]*.

In the BREAK-3 study, the incidence of fever (serious and non-serious) was 28% in patients receiving TAFINLAR and 10% in patients receiving dacarbazine. In patients receiving TAFINLAR, the median time to initial onset of fever (any severity) was 11 days (range: 1 day to 6.6 months) and the median duration of fever was 3 days (range: 1 day to 4.2 months). Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills occurred in 3.7% (7/187) of patients receiving TAFINLAR and in none of the 59 patients receiving dacarbazine.

In the COMBI-d and COMBI-v studies, fever occurred in 54% (303/559) of patients receiving TAFINLAR with trametinib; the median time to onset of first occurrence of fever was 1 month (range: 1 day to 23.5 months) and

the median duration of fever was 3 days (range: 1 day to 11.3 months). Approximately one-half of the patients who received TAFINLAR with trametinib and experienced pyrexia had 3 or more discrete episodes.

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 with melanoma receiving TAFINLAR with trametinib. 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.

Withhold TAFINLAR for fever of 101.3ºF or higher. Withhold TAFINLAR 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 Table 2 for recommended dose modifications for adverse reactions *[see Dosage and Administration (2.3)]*. Administer antipyretics as secondary prophylaxis when resuming TAFINLAR if patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (e.g., 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.

5.7 Serious Skin Toxicity

Serious skin toxicity can occur with TAFINLAR.

Across clinical trials of TAFINLAR administered with trametinib (N = 559) in patients with melanoma, serious skin toxicity occurred in 0.7% (4/559) of patients.

Withhold TAFINLAR for intolerable or severe skin toxicity. TAFINLAR may be resumed at the next lower dose level in patients with improvement or recovery from skin toxicity within 3 weeks *[see Dosage and Administration (2.3)]*.

5.8 Hyperglycemia

Hyperglycemia can occur with TAFINLAR.

In the BREAK-3 study, 5 of 12 patients with a history of diabetes required more intensive hypoglycemic therapy receiving TAFINLAR. The incidence of Grade 3 hyperglycemia based on laboratory values was 6% (12/187) in patients receiving TAFINLAR compared with none of the dacarbazine-treated patients.

In the COMBI-d study, 27% (4/15) of patients with a history of diabetes receiving TAFINLAR with trametinib and 13% (2/16) of patients with a history of diabetes receiving single-agent TAFINLAR required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia based on laboratory values occurred in 5% (11/208) and 0.5% (1/208) of patients, respectively, receiving TAFINLAR with trametinib compared with 4.3% (9/209) for Grade 3 hyperglycemia and no patients with Grade 4 hyperglycemia for patients receiving single-agent TAFINLAR.

Monitor serum glucose levels upon initiation and as clinically appropriate when TAFINLAR is administered in patients with pre-existing diabetes or hyperglycemia.

5.9 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. Monitor patients with G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR.

5.10 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended clinical dose. If TAFINLAR is used during pregnancy or if the patient becomes pregnant while taking TAFINLAR, advise the patient of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

Advise female patients of reproductive potential to use an effective non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the last dose of TAFINLAR. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Drug Interactions (7.2), Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in another section of the label:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Tumor Promotion in BRAF Wild-Type Melanoma *[see Warnings and Precautions (5.2)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Cardiomyopathy *[see Warnings and Precautions (5.4)]*
- Uveitis *[see Warnings and Precautions (5.5)]*
- Serious Febrile Reactions *[see Warnings and Precautions (5.6)]*
- Serious Skin Toxicity *[see Warnings and Precautions (5.7)]*
- Hyperglycemia *[see Warnings and Precautions (5.8)]*
- Glucose-6-Phosphate Dehydrogenase Deficiency *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

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

The data described in the Warnings and Precautions section reflect exposure to TAFINLAR administered as a single agent in 586 patients with various solid tumors and exposure to TAFINLAR administered with trametinib in 559 patients with melanoma and 93 patients with NSCLC. The safety of TAFINLAR as a single agent was evaluated in 586 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range: 118 to 300 mg).

Metastatic or Unresectable BRAF V600 Mutation Positive Melanoma

TAFINLAR as a Single Agent

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of the BREAK-3 study *[see Clinical Studies (14.1)]*.This study, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m^2 intravenously every 3 weeks (n = 63). The trial excluded patients with abnormal left ventricular ejection fraction or cardiac valve morphology (≥ Grade 2), corrected QT interval greater than or equal to 480 milliseconds on electrocardiogram, or a known history of glucose-6-phosphate dehydrogenase deficiency. The median duration on treatment was 4.9 months for patients treated with TAFINLAR and 2.8 months for dacarbazine-treated patients. The population exposed to TAFINLAR was 60% male, 99% White, and had a median age of 53 years.

The most commonly occurring adverse reactions (≥20%) in patients treated with TAFINLAR were, in order of decreasing frequency: hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome (PPES).

The incidence of adverse events resulting in permanent discontinuation of study medication in the BREAK-3 study was 3% for patients treated with TAFINLAR and 3% for patients treated with dacarbazine. The most frequent (≥2%) adverse reactions leading to dose reduction of TAFINLAR were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%).

Table 3. Select Common Adverse Reactions Occurring in ≥10% (All Grades) or ≥2% (Grades 3 or 4) of Patients Treated with TAFINLAR in the BREAK-3 Study[a]

Adverse Reactions	TAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and subcutaneous tissue				
Hyperkeratosis	37	1	0	0
Alopecia	22	NA[f]	2	NA[f]
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system				
Headache	32	0	8	0
General disorders				
Pyrexia	28	3	10	0
Musculoskeletal				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	0	0
Neoplasms				
Papilloma[c]	27	0	2	0
cuSCC[d, e]	7	4	0	0
Respiratory				
Cough	12	0	5	0
Gastrointestinal				
Constipation	11	2	14	0
Infections				
Nasopharyngitis	10	0	3	0

[a] Adverse drug reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.
[b] Grade 4 adverse reactions limited to hyperkeratosis (n = 1) and constipation (n = 1).
[c] Includes skin papilloma and papilloma.
[d] cuSCC = cutaneous squamous cell carcinoma, includes squamous cell carcinoma of the skin and keratoacanthoma.
[e] Cases of cuSCC were required to be reported as Grade 3 per protocol.
[f] NA = not applicable.

Table 4. Incidence of Laboratory Abnormalities Increased from Baseline Occurring at a Higher Incidence in Patients Treated with TAFINLAR in 1the BREAK-3 Study [Between-Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3 or 4)][a]

	TAFINLAR N = 187		DTIC N = 59	
Test	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6[b]	14	2
Increased alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

[a] Adverse drug reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.
[b] Grade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

Other clinically important adverse reactions observed in less than 10% of patients (N = 586) treated with TAFINLAR were:

Gastrointestinal Disorders: Pancreatitis

Immune System Disorders: Hypersensitivity manifesting as bullous rash

Renal and Urinary Disorders: Interstitial nephritis

TAFINLAR Administered with Trametinib

The safety of TAFINLAR when administered with trametinib was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600E or V600K mutation-positive melanoma who received TAFINLAR in two trials, the COMBI-d study (n = 209) a multicenter, double-blind, randomized (1:1), active controlled trial and the COMBI-v study (n = 350) a multicenter, open-label, randomized (1:1), active controlled trial. In the COMBI-d and COMBI-v studies, patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. Both trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of RVO or RPED, QTcB interval ≥480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, or a known history of G6PD deficiency *[see Clinical Studies (14.2)]*.

Among these 559 patients, 199 (36%) were exposed to TAFINLAR for >6 months to 12 months while 185 (33%) were exposed to TAFINLAR for ≥1 year. The median age was 55 years (range: 18 to 91), 57% were male, 98% were White, 72% had baseline ECOG performance status 0 and 28% had ECOG performance status 1, 64% had M1c stage disease, 35% had elevated LDH at baseline and 0.5% had a history of brain metastases.

The most commonly occurring adverse reactions (≥20%) for TAFINLAR in patients receiving TAFINLAR plus trametinib in the COMBI-d and COMBI-v studies were: pyrexia, rash, chills, headache, arthralgia, and cough.

Table 5 and Table 6 present adverse drug reactions and laboratory abnormalities, respectively, observed in the COMBI-d study.

The demographics and baseline tumor characteristics of patients enrolled in the COMBI-d study are summarized in Clinical Studies *[see Clinical Studies (14.2)]*. Patients receiving TAFINLAR plus trametinib had a median duration of exposure of 11 months (range: 3 days to 30 months) to TAFINLAR. Among the 209 patients receiving TAFINLAR plus trametinib, 26% were exposed to TAFINLAR for >6 months to 12 months while 46% were exposed to TAFINLAR for >1 year.

In the COMBI-d study, adverse reactions resulting in discontinuation of TAFINLAR occurred in 11% of patients receiving TAFINLAR plus trametinib; the most common was pyrexia (1.9%). Adverse reactions leading to dose reductions of TAFINLAR occurred in 26% of patients receiving TAFINLAR plus trametinib; the most common 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 receiving TAFINLAR plus trametinib; the most common were pyrexia (35%), chills (11%), vomiting (7%), nausea (5%), and decreased ejection fraction (5%).

Table 5. Select Adverse Reactions Occurring in ≥10% (All Grades) of Patients Treated with TAFINLAR in Combination with Trametinib in the COMBI-d Study[a]

Adverse Reactions	Pooled TAFINLAR plus Trametinib N = 559		COMBI-d Study			
			TAFINLAR plus Trametinib N = 209		TAFINLAR N = 211	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Gastrointestinal						
Constipation	13	0.2	13	0.5	10	0
Nervous system						
Headache	30	0.9	33	0.5	30	1.4
Dizziness	11	0.2	14	0	7	0
Musculoskeletal						
Arthralgia	25	0.9	26	0.9	31	0
Myalgia	15	0.2	13	0.5	13	0
Skin						
Rash[c]	32	1.1	42	0	27	1.4
Dry skin	10	0	12	0	16	0
Respiratory						
Cough	20	0	21	0	21	0
Infections						
Nasopharyngitis	12	0	12	0	10	0

[a] NCI CTCAE version 4.0.
[b] Grade 4 adverse reactions limited to headache (n = 1).
[c] Includes rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, rash maculo-papular, and rash folliculitis.

Other clinically important adverse reactions for TAFINLAR across the COMBI-d and COMBI-v studies (N = 559) observed in less than 10% of patients receiving TAFINLAR in combination with trametinib were:

Gastrointestinal Disorders: Pancreatitis

Subcutaneous Tissue Disorders: Panniculitis

Table 6. Select Treatment-Emergent Laboratory Abnormalities Occurring at ≥10% (All Grades) of Patients Receiving TAFINLAR with Trametinib in the COMBI-d Study

Test	Pooled TAFINLAR plus Trametinib N = 559[a]		COMBI-d Study			
			TAFINLAR plus Trametinib N = 209[b]		TAFINLAR N = 211[b]	
	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)
Liver Function Tests						
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypophosphatemia	38	6	38	3.8	35	7
Hyponatremia	25	8	24	6	14	2.9

[a] For these laboratory tests the denominator is 556.
[b] For these laboratory tests the denominator is 208 for the combination arm, 208-209 for the TAFINLAR arm.
[c] Grade 4 adverse reactions limited to hyperglycemia (n = 4), hyponatremia and hypophosphatemia (each n = 1), in the pooled combination arm; hyperglycemia (n = 1) in the COMBI-d study combination arm; hypophosphatemia (n = 1) in the TAFINLAR arm.

Metastatic, BRAF V600E-Mutation Positive, Non-Small Cell Lung Cancer (NSCLC)

The safety of TAFINLAR when administered with trametinib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BRF113928). Patients received TAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. The trial excluded patients with abnormal left ventricular ejection fraction, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), QTc interval ≥480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, history of interstitial lung disease or pneumonitis, or history or current retinal vein occlusion *[see Clinical Studies (14.3)]*.

Among these 93 patients, 53 (57%) were exposed to TAFINLAR and trametinib for >6 months and 27 (29%) were exposed to TAFINLAR and trametinib for ≥1 year. The median age was 65 years (range: 41 to 91); 46% were male; 85% were White; 32% had baseline ECOG performance status 0 and 61% had ECOG performance status 1; 98% had non-squamous histology; and 12% were current smokers, 60% were former smokers, and 28% had never smoked.

The most commonly occurring adverse reactions (≥20%) in these 93 patients were: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.

Adverse reactions resulting in discontinuation of TAFINLAR occurred in 18% of patients; the most common were pyrexia (2.2%), ejection fraction decreased (2.2%), and respiratory distress (2.2%). Adverse reactions leading to dose reductions of TAFINLAR occurred in 35% of patients; the most common were pyrexia (10%), diarrhea (4.3%), nausea (4.3%), vomiting (4.3%), and neutropenia (3.2%). Adverse reactions leading to dose interruptions of TAFINLAR occurred in 62% of patients; the most common were pyrexia (27%), vomiting (11%), neutropenia (8%), and chills (6%).

Table 7 and Table 8 present adverse drug reactions and laboratory abnormalities, respectively, of TAFINLAR in Study BRF113928.

Table 7. Adverse Reactions Occurring in ≥20% (All Grades) of Patients Treated with TAFINLAR in Combination with Trametinib in Study BRF113928[a]

Adverse Reactions	TAFINLAR plus Trametinib N = 93	
	All Grades (%)	Grades 3 and 4[b] (%)
General		
Pyrexia	55	5
Fatigue[b]	51	5
Edema[c]	28	0
Chills	23	1.1
Gastrointestinal		
Nausea	45	0
Vomiting	33	3.2
Diarrhea	32	2.2
Decreased appetite	29	0
Respiratory system		
Cough	22	0
Dyspnea	20	5
Skin		
Dry skin	31	1.1
Rash[d]	28	3.2
Vascular		
Hemorrhage[e]	23	3.2

[a] NCI CTCAE version 4.0.
[b] Includes fatigue, malaise, and asthenia
[c] Includes peripheral edema, edema, and generalized edema.
[d] Includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.
[e] Includes hemoptysis, hematoma, epistaxis, purpura, hematuria, subarachnoid hemorrhage, gastric hemorrhage, urinary bladder hemorrhage, contusion, hematochezia, injection site hemorrhage, pulmonary hemorrhage, and retroperitoneal hemorrhage.

Other clinically important adverse reactions for TAFINLAR observed in less than 10% of patients with NSCLC receiving TAFINLAR in combination with trametinib were:

Gastrointestinal Disorders: Pancreatitis

Renal and Urinary Disorders: Tubulointerstitial nephritis

Table 8. Treatment-Emergent Laboratory Abnormalities Occurring in ≥20% (All Grades) of Patients Receiving TAFINLAR with Trametinib in Study BRF113928

Test	TAFINLAR plus Trametinib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
Hematology[a]		
Leukopenia	48	8
Anemia	46	10
Neutropenia	44	8
Lymphopenia	42	14
Liver Function Tests[b]		
Increased blood alkaline phosphatase	64	0
Increased AST	61	4.4
Increased ALT	32	6
Chemistry[b]		
Hyperglycemia	71	9
Hyponatremia	57	17
Hypophosphatemia	36	7
Increased creatinine	21	1.1

[a] For these laboratory tests the denominator is 91.
[b] For these laboratory tests the denominator is 90.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Dabrafenib

Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors of CYP3A4 or CYP2C8 may increase concentrations of dabrafenib *[see Clinical Pharmacology (12.3)]*. Substitution of strong inhibitors of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, gemfibrozil) of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors.

7.2 Effects of Dabrafenib on Other Drugs

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate) *[see Clinical Pharmacology (12.3)]*. Monitor international normalized ratio (INR) levels more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib. Coadministration of TAFINLAR with other substrates of these enzymes, including dexamethasone or hormonal contraceptives, can result in decreased concentrations and loss of efficacy *[see Use in Specific Populations (8.1, 8.3)]*. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies and its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There is insufficient data in pregnant women exposed to TAFINLAR to assess the risks. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended clinical dose of 150 mg twice daily

[see Data]. If TAFINLAR is used during pregnancy or if the patient becomes pregnant while taking TAFINLAR, advise the patient of the potential risk to a fetus.

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

Data

Animal Data: In a combined female fertility and embryo-fetal development study in rats conducted during the period of organogenesis, developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape at a dabrafenib dose of 300 mg/kg/day (approximately three times the human exposure at the recommended dose based on AUC). At doses of 20 mg/kg/day or greater (equivalent to the human exposure at the recommended dose based on AUC), rats demonstrated delays in skeletal development and reduced fetal body weight.

8.2 Lactation

Risk Summary

There are no data on the presence of dabrafenib in human milk, or the effects of dabrafenib on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions from TAFINLAR in breastfed infants, advise women not to breastfeed during treatment with TAFINLAR and for 2 weeks following the last dose of TAFINLAR.

8.3 Females and Males of Reproductive Potential

Based on data from animal studies and its mechanism of action, TAFINLAR can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with TAFINLAR and for 2 weeks after the last dose of TAFINLAR. Counsel patients to use a non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective *[see Drug Interactions (7.1)]*. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR.

Infertility

Females

Advise female patients of reproductive potential that TAFINLAR may impair fertility. A reduction in fertility was observed in female rats at dose exposures equivalent to the human exposure at the recommended dose. A reduction in the number of corpora lutea was noted in pregnant rats at dose exposures approximately three times the human exposure at the recommended dose *[see Nonclinical Toxicology (13.1)]*.

Males

Advise male patients of the potential risk for impaired spermatogenesis which may be irreversible. Effects on spermatogenesis have been observed in animals treated with dabrafenib at dose exposures up to three times the human exposure at the recommended dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of TAFINLAR as a single agent or with trametinib have not been established in pediatric patients.

Juvenile Animal Data

In a repeat-dose toxicity study in juvenile rats, an increased incidence of kidney cysts and tubular deposits were noted at doses as low as 0.2 times the human exposure at the recommended adult dose based on AUC.

Additionally, forestomach hyperplasia, decreased bone length, and early vaginal opening were noted at doses as low as 0.8 times the human exposure at the recommended adult dose based on AUC.

8.5 Geriatric Use

One hundred and twenty-six (22%) of 586 patients in clinical trials of TAFINLAR administered as a single agent and 40 (21%) of the 187 patients receiving TAFINLAR in the BREAK-3 study were greater than or equal to 65 years of age. No overall differences in the effectiveness or safety of TAFINLAR were observed in elderly patients as compared to younger patients in the BREAK-3 study.

Of the 559 patients with melanoma randomized to receive TAFINLAR plus trametinib in the COMBI-d and COMBI-v studies, 24% were aged 65 years and older and 6% patients aged 75 years and older. No overall differences in the effectiveness of TAFINLAR plus trametinib were observed in elderly patients as compared to younger patients. The incidences of peripheral edema (26% vs. 12%) and anorexia (21% vs. 9%) were increased in elderly patients as compared to younger patients.

Clinical studies of TAFINLAR in NSCLC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

No formal pharmacokinetic trial in patients with hepatic impairment has been conducted. Dose adjustment is not recommended for patients with mild hepatic impairment based on the results of the population pharmacokinetic analysis. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, patients with moderate to severe hepatic impairment may have increased exposure. An appropriate dose has not been established for patients with moderate to severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

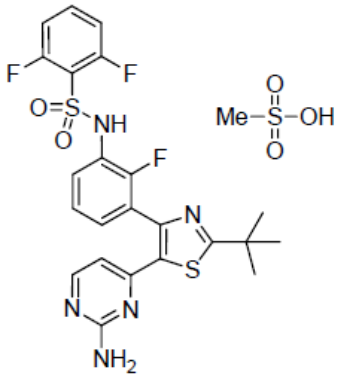
No formal pharmacokinetic trial in patients with renal impairment has been conducted. Dose adjustment is not recommended for patients with mild or moderate renal impairment based on the results of the population pharmacokinetic analysis. An appropriate dose has not been established for patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no information on overdosage of TAFINLAR. Since dabrafenib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with TAFINLAR.

11 DESCRIPTION

Dabrafenib mesylate is a kinase inhibitor. The chemical name for dabrafenib mesylate is N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt. It has the molecular formula $C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_4O_3S$ and a molecular weight of 615.68. Dabrafenib mesylate has the following chemical structure:



Dabrafenib mesylate is a white to slightly colored solid with three pK_as: 6.6, 2.2, and -1.5. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

TAFINLAR (dabrafenib) capsules are supplied as 50 mg and 75 mg capsules for oral administration. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Each 75 mg capsule contains 88.88 mg dabrafenib mesylate equivalent to 75 mg of dabrafenib free base.

The inactive ingredients of TAFINLAR are colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC_{50} values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC_{50} values of 3.2 and 5.0 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth *[see Indications and Usage (1)]*. Dabrafenib inhibits cell growth of various BRAF V600 mutation-positive tumors in vitro and in vivo.

Dabrafenib and trametinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive tumor xenografts compared with either drug alone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The potential effect of TAFINLAR on QT prolongation was assessed in a dedicated multiple-dose study in 32 patients with BRAF V600 mutation-positive tumors. No large changes in the mean QT interval (i.e., >20 ms) were detected with dabrafenib 300 mg administered twice daily (two times the recommended dosage).

In clinical trials, QTc (heart rate-corrected QT) prolongation to ≥500 ms occurred in 0.8% (2/264) of patients receiving TAFINLAR plus trametinib and in 1.5 % (4/264) of patients receiving TAFINLAR as a single agent. The QTc was increased >60 ms from baseline in 3.8% (10/264) of patients receiving TAFINLAR plus trametinib and 3% (8/264) of patients treated with TAFINLAR as a single agent.

12.3 Pharmacokinetics

Absorption

After oral administration, median time to achieve peak plasma concentration (T_{max}) is 2 hours. Mean absolute bioavailability of oral dabrafenib is 95%. Following a single dose, dabrafenib exposure (C_{max} and AUC) increased in a dose-proportional manner across the dose range of 12 to 300 mg, but the increase was less than dose-proportional after repeat twice-daily dosing. After repeat twice-daily dosing of 150 mg, the mean accumulation ratio was 0.73 and the inter-subject variability (CV%) of AUC at steady-state was 38%.

Administration of dabrafenib with a high-fat meal decreased C_{max} by 51%, decreased AUC by 31%, and delayed median T_{max} by 3.6 hours as compared with the fasted state *[see Dosage and Administration (2.2)]*.

Distribution

Dabrafenib is 99.7% bound to human plasma proteins. The apparent volume of distribution (V_c/F) is 70.3 L.

Metabolism

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib. Hydroxy-dabrafenib is further oxidized via CYP3A4 to form carboxy-dabrafenib and subsequently excreted in bile and urine. Carboxy-dabrafenib is decarboxylated to form desmethyl-dabrafenib; desmethyl-dabrafenib may be reabsorbed from the gut. Desmethyl-dabrafenib is further metabolized by CYP3A4 to oxidative metabolites. Mean metabolite-to-parent AUC ratios following repeat-dose administration are 0.9, 11, and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on systemic exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib.

Elimination

The mean terminal half-life of dabrafenib is 8 hours after oral administration. Hydroxy-dabrafenib terminal half-life (10 hours) parallels that of dabrafenib while the carboxy- and desmethyl-dabrafenib metabolites exhibit longer half-lives (21 to 22 hours). The apparent clearance of dabrafenib is 17.0 L/h after single dosing and 34.4 L/h after 2 weeks of twice-daily dosing.

Fecal excretion is the major route of elimination accounting for 71% of radioactive dose while urinary excretion accounted for 23% of total radioactivity as metabolites only.

Specific Populations

Age, Body Weight, and Gender: Based on the population pharmacokinetics analysis, age has no effect on dabrafenib pharmacokinetics. Pharmacokinetic differences based on gender and on weight are not clinically relevant.

Pediatric: Pharmacokinetics of dabrafenib has not been studied in pediatric patients.

Renal Impairment: No formal pharmacokinetic trial in patients with renal impairment has been conducted. The pharmacokinetics of dabrafenib were evaluated using a population analysis in 233 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 m^2) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m^2) enrolled in clinical trials. Mild or moderate renal impairment has no effect on systemic exposure to dabrafenib and its metabolites. No data are available in patients with severe renal impairment.

Hepatic Impairment: No formal pharmacokinetic trial in patients with hepatic impairment has been conducted. The pharmacokinetics of dabrafenib was evaluated using a population analysis in 65 patients with mild hepatic impairment enrolled in clinical trials. Mild hepatic impairment has no effect on systemic exposure to dabrafenib and its metabolites. No data are available in patients with moderate to severe hepatic impairment.

Drug Interactions

Effect of Strong Inhibitors of CYP3A4 or CYP2C8 on Dabrafenib: In vitro studies show that dabrafenib is a substrate of CYP3A4 and CYP2C8 while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4

substrates. Coadministration of dabrafenib 75 mg twice daily and ketoconazole 400 mg once daily (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%. Coadministration of dabrafenib 75 mg twice daily and gemfibrozil 600 mg twice daily (a strong CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of dabrafenib metabolites.

Effect of Strong Inducers of CYP3A4 or Moderate Inducers CYP2C8 on Dabrafenib: Coadministration of dabrafenib 150 mg twice daily and rifampin 600 mg once daily (a strong CYP3A4 and moderate CYP2C8 inducer) for 10 days decreased dabrafenib AUC by 34%, had no effect on hydroxy-dabrafenib AUC, and decreased desmethyl-dabrafenib AUC by 30%.

Effect of Dabrafenib on CYP Substrates: In vitro data demonstrate that dabrafenib is an inducer of CYP3A4 and CYP2B6 via activation of the pregnane X receptor (PXR) and constitutive androstane receptor (CAR) nuclear receptors. Dabrafenib may also induce CYP2C enzymes via the same mechanism. Coadministration of TAFINLAR 150 mg twice daily for 15 days and a single dose of midazolam 3 mg (a CYP3A4 substrate) decreased midazolam AUC by 65%. Coadministration of dabrafenib 150 mg twice daily for 15 days and a single dose of warfarin 15 mg decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin (a CYP3A4/CYP1A2 substrate) by 33%.

Effect of Transporters on Dabrafenib: Dabrafenib and its metabolites, hydroxyl-dabrafenib and desmethyl-dabrafenib, are substrates of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but are not substrates of organic cation transporter (OCT1) or organic anion transporting polypeptide (OATP1A2, OATP1B1, OATP1B3, OATP2B1) in vitro.

Effect of Dabrafenib on Transporters: Dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib, are inhibitors of OATP1B1, OATP1B3 and organic anion transporter (OAT1 and OAT3) in vitro. Dabrafenib and desmethyl-dabrafenib are inhibitors of OCT2 and BCRP in vitro. Coadministration of TAFINLAR 150 mg twice daily with a single dose of rosuvastatin (a sensitive OATP1B1 and OATP1B3 substrate) increased rosuvastatin C_{max} by 2.6-fold, but did not change its AUC.

Effect of Trametinib on Dabrafenib: Coadministration of trametinib 2 mg daily with dabrafenib 150 mg twice daily resulted in a 23% increase in AUC of dabrafenib, a 33% increase in AUC of desmethyl-dabrafenib, and no change in AUC of hydroxy-dabrafenib as compared with administration of dabrafenib.

Effect of Acid Reducing Agents on Dabrafenib: Coadministration of dabrafenib 150 mg twice daily and rabeprazole 40 mg once daily for 4 days resulted in a 3% increase in AUC of dabrafenib, a 15% decrease in AUC of desmethyl-dabrafenib, and a 5% increase in AUC of hydroxy-dabrafenib as compared to administration of dabrafenib alone. The changes in exposure of dabrafenib and its metabolites were not clinically relevant.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with dabrafenib have not been conducted. TAFINLAR increased the risk of cutaneous squamous cell carcinomas in patients in clinical trials.

Dabrafenib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay, and was not clastogenic in an in vivo rat bone marrow micronucleus test.

In a combined female fertility and embryo-fetal development study in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant females at 300 mg/kg/day (which is approximately three times the human exposure at the recommended dose based on AUC).

Male fertility studies with dabrafenib have not been conducted; however, in repeat-dose studies, testicular degeneration/depletion was seen in rats and dogs at doses equivalent to and three times the human exposure at the recommended dose based on AUC, respectively.

13.2 Animal Toxicology and/or Pharmacology

Adverse cardiovascular effects were noted in dogs at dabrafenib doses of 50 mg/kg/day (approximately five times the human exposure at the recommended dose based on AUC) or greater, when administered for up to 4 weeks. Adverse effects consisted of coronary arterial degeneration/necrosis and hemorrhage, as well as cardiac atrioventricular valve hypertrophy/hemorrhage.

14 CLINICAL STUDIES

14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma – TAFINLAR Administered as a Single Agent

In the BREAK-3 study (NCT01227889), the safety and efficacy of TAFINLAR as a single agent were demonstrated in an international, multicenter, randomized (3:1), open-label, active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. Patients were randomized to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m^2 intravenously every 3 weeks (n = 63). Randomization was stratified by disease stage at baseline [unresectable Stage III (regional nodal or in-transit metastases), M1a (distant skin, subcutaneous, or nodal metastases), or M1b (lung metastases) versus M1c melanoma (all other visceral metastases or elevated serum LDH)]. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. In addition, an independent radiology review committee (IRRC) assessed the following efficacy outcome measures in pre-specified supportive analyses: PFS, confirmed objective response rate (ORR), and duration of response.

The median age of patients in the BREAK-3 study was 52 years. The majority of the trial population was male (60%), White (99%), had an ECOG performance status of 0 (67%), M1c disease (66%), and normal LDH (62%). All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were tested retrospectively, using an FDA-approved companion diagnostic test, THxID™-BRAF assay.

The median durations of follow-up prior to initiation of alternative treatment in patients randomized to receive TAFINLAR was 5.1 months and in the dacarbazine arm was 3.5 months. Twenty-eight (44%) patients crossed over from the dacarbazine arm at the time of disease progression to receive TAFINLAR.

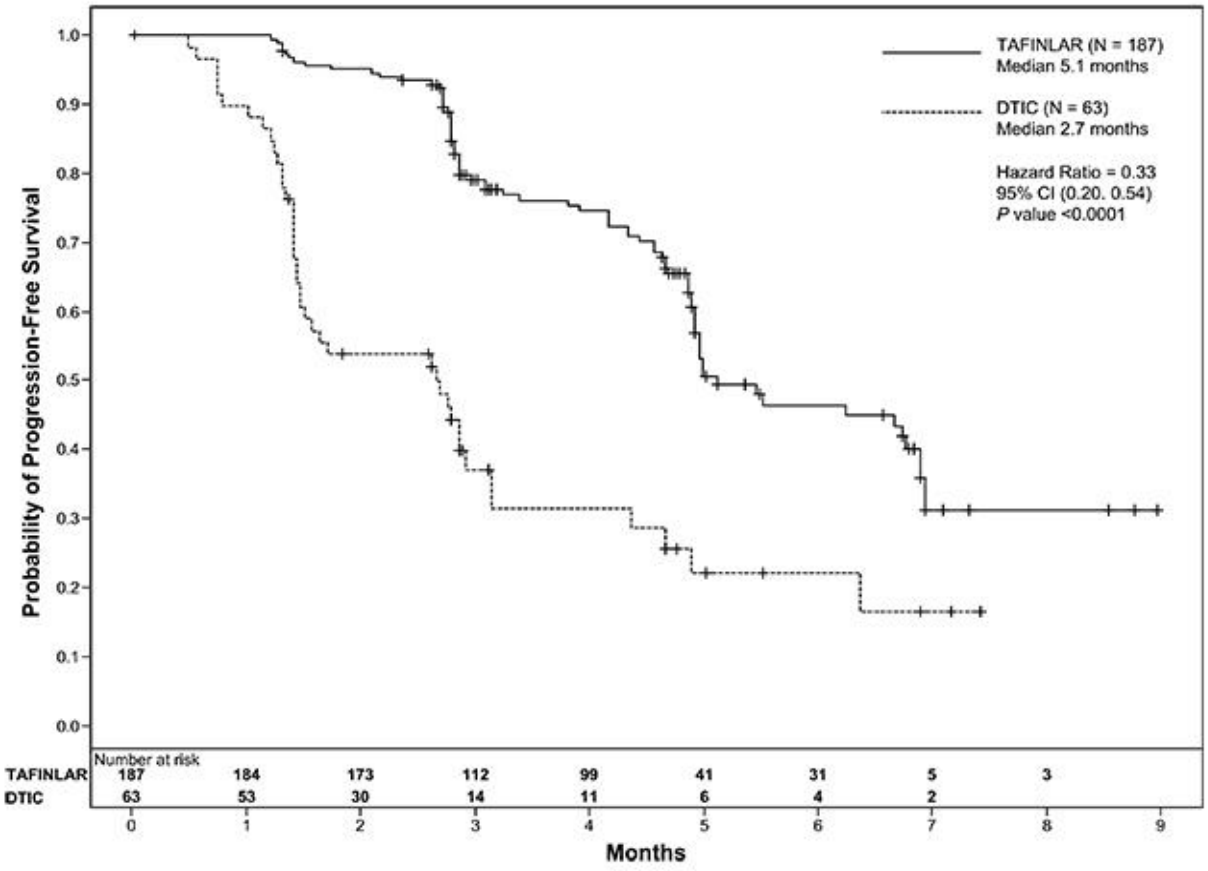
The BREAK-3 study demonstrated a statistically significant increase in progression-free survival in the patients treated with TAFINLAR. Table 9 and Figure 1 summarize the PFS results.

Table 9. Investigator-Assessed Progression-Free Survival and Confirmed Objective Response Results in the BREAK-3 Study

Investigator-Assessed Endpoints†	TAFINLAR N = 187	Dacarbazine N = 63
Progression-Free Survival		
Number of Events (%)	78 (42%)	41 (65%)
Progressive Disease	76	41
Death	2	0
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR[a] (95% CI)	0.33 (0.20, 0.54)	
P-value[b]	<0.0001	
Confirmed Tumor Responses		
Objective Response Rate	52%	17%
(95% CI)	(44, 59)	(9, 29)
CR, n (%)	6 (3%)	0
PR, n (%)	91 (48%)	11 (17%)
Duration of Response		
Median, months (95% CI)	5.6 (5.4, NR)	NR (5.0, NR)

† CI = Confidence interval; HR = Hazard ratio; CR = Complete response; PR = Partial response; NR = Not reached.
[a] Pike estimator, stratified by disease state.
[b] Stratified log-rank test.

Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival in the BREAK-3 Study



In supportive analyses based on IRRC assessment and in an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma with the THxID™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis.

The activity of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, open-label, two-cohort multicenter trial. All patients received TAFINLAR 150 mg twice daily. Patients in Cohort A (n = 74) had received no prior local therapy for brain metastases, while patients in Cohort B (n = 65) had received at least one local therapy for brain metastases, including, but not limited to, surgical resection, whole brain radiotherapy, or stereotactic radiosurgery such as gamma knife, linear-accelerated-based radiosurgery, or charged particles. In addition, patients in Cohort B were required to have evidence of disease progression in a previously treated lesion or an untreated lesion. Additional eligibility criteria were at least one measurable lesion of 0.5 cm or greater in largest diameter on contrast-enhanced MRI, stable or decreasing corticosteroid dose, and no more than two prior systemic regimens for treatment of metastatic disease. The primary outcome measure was estimation of the overall intracranial response rate (OIRR) in each cohort.

The median age of patients in Cohort A was 50 years, 72% were male, 100% were White, 59% had a pre-treatment ECOG performance status of 0, and 57% had an elevated LDH value at baseline. The median age of patients in Cohort B was 51 years, 63% were male, 98% were White, 66% had a pre-treatment ECOG performance status of 0, and 54% had an elevated LDH value at baseline. Efficacy results as determined by an independent radiology review committee, masked to investigator response assessments, are provided in Table 10.

Table 10. Efficacy Results in Patients with BRAF V600E Melanoma Brain Metastases

IRRC-assessed Endpoints	Cohort A n = 74	Cohort B n = 65
Overall Intracranial Response Rate (OIRR)		
% (95% CI)	18 (9.7, 28.2)	18 (9.9, 30.0)
Duration of OIRR	(n = 13)	(n = 12)
Median, months (95% CI)	4.6 (2.8, NR)	4.6 (1.9, 4.6)

IRRC = Independent radiology review committee; CI = Confidence interval; NR = Not reached.

14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – TAFINLAR Administered with Trametinib

The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one open-label trial (the COMBI-v study; NCT01597908).

The COMBI-d study compared TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or TAFINLAR 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

The COMBI-v study compared TAFINLAR and trametinib to vemurafenib as first-line treatment therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was overall survival. Additional efficacy outcome measures were PFS and ORR as assessed by investigator per RECIST v1.1.

In the COMBI-d study, 423 patients were randomized to TAFINLAR plus trametinib (n = 211) or TAFINLAR plus placebo (n = 212). The median age was 56 years (range: 22 to 89 years), 53% were male, >99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIC, 66% had M1c disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing, 85% with BRAF V600E mutations and 15% with BRAF V600K mutations.

In the COMBI-v study, 704 patients were randomized to TAFINLAR plus trametinib (n = 352) or single-agent vemurafenib (n = 352). The median age was 55 years (range: 18 to 91 years), 96% were White, and 55% were male, 6% percent of patients had Stage IIIC, 61% had M1c disease, 67% had a normal LDH, 70% had ECOG performance status of 0, 89% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases.

The COMBI-d and COMBI-v studies demonstrated statistically significant improvements in OS and PFS (see Table 11 and Figures 2 and 3).

Table 11. Efficacy Results in Patients with BRAF V600E or V600K Melanoma[a]

Endpoint[†]	COMBI-d Study		COMBI-v Study	
	TAFINLAR plus Trametinib N = 211	**TAFINLAR plus Placebo N = 212**	**TAFINLAR plus Trametinib N = 352**	**Vemurafenib N = 352**
Overall Survival				
Number of deaths (%)	99 (47%)	123 (58%)	100 (28%)	122 (35%)
Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.1)	NR (18.3, NR)	17.2 (16.4, NR)
HR (95% CI)	0.71 (0.55, 0.92)		0.69 (0.53, 0.89)	
P value (log-rank test)	0.01		0.005[a]	
Progression-Free Survival (PFS)[b]				
Number of events (%)	102 (48%)	109 (51%)	166 (47%)	217 (62%)
Median, months (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
HR (95% CI)	0.75 (0.57, 0.99)		0.56 (0.46, 0.69)	
P value (log-rank test)	0.035		<0.001	
Overall Response Rate (ORR)[b]				
ORR, % (95% CI)	66 (60, 73)	51 (44, 58)	64 (59, 69)	51 (46, 56)
P value	<0.001		<0.001	
CR, %	10	8	13	8
PR, %	56	42	51	43
Median duration of response, months (95% CI)	9.2 (7.4, NR)	10.2 (7.5, NR)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

[†] CI = Confidence interval; HR = Hazard ratio; CR = Complete response; PR = Partial response; NR = Not reached.
[a] P-value is comparing with the allocated alpha of 0.021 for the interim analysis based on 77% information.
[b] PFS and ORR were assessed by investigator.

Figure 2. Kaplan-Meier Curves for Overall Survival in the COMBI-d Study

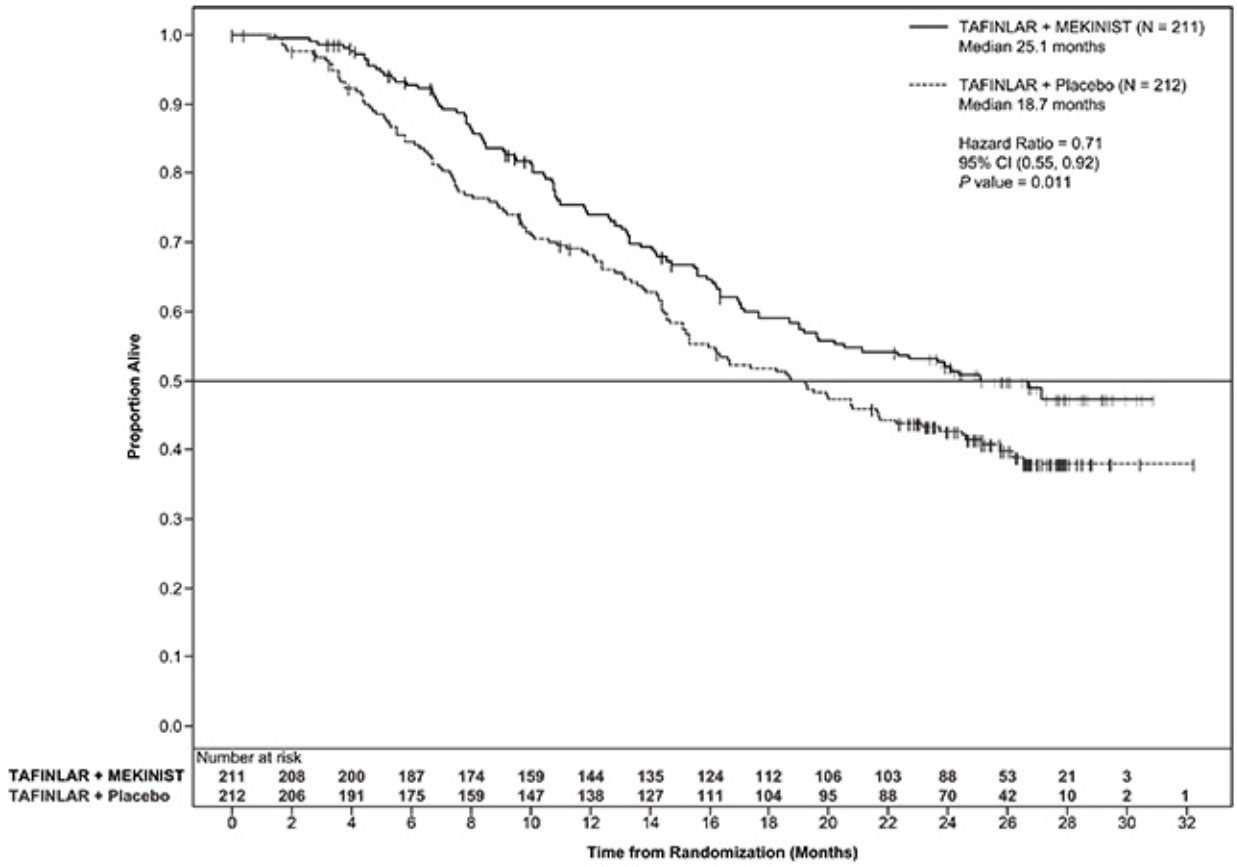
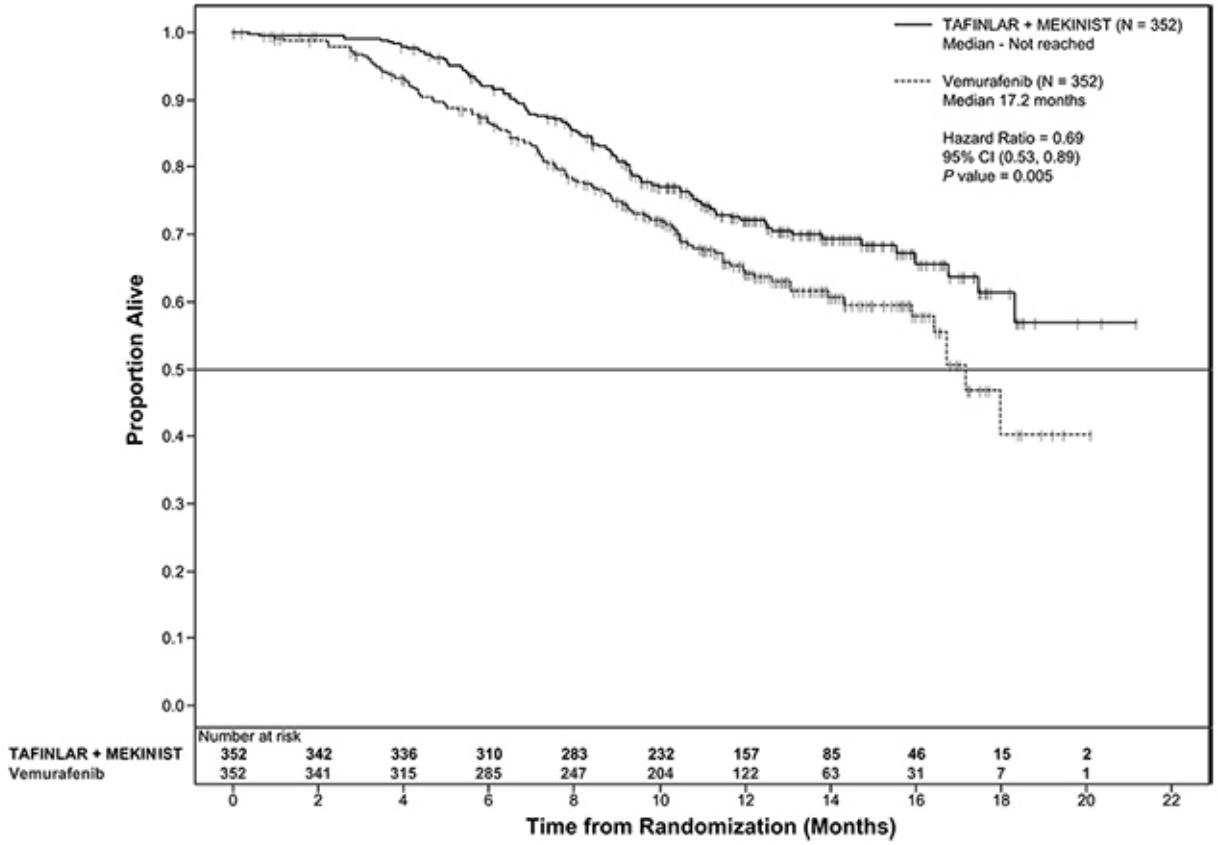


Figure 3. Kaplan-Meier Curves for Overall Survival in the COMBI-v Study



14.3 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

In Study BRF113928 (NCT01336634), the safety and efficacy of TAFINLAR alone or administered with trametinib were evaluated in a multi-center, three-cohort, non-randomized, activity-estimating, open-label trial. Key eligibility criteria were locally confirmed BRAF V600E mutation-positive metastatic NSCLC, no prior exposure to BRAF or MEK-inhibitor, and absence of EGFR mutation or ALK rearrangement (unless patients had progression on prior tyrosine kinase inhibitor therapy). Patients enrolled in Cohorts A and B were required to have received at least one previous platinum based chemotherapy regimen for NSCLC with demonstrated disease progression but no more than three prior systemic regimens. Patients enrolled in Cohort C could not have received prior systemic therapy for metastatic NSCLC. Patients in Cohort A received TAFINLAR 150 mg twice daily. Patients in Cohorts B and C received TAFINLAR 150 mg twice daily and trametinib 2 mg once daily. The major efficacy outcome measure was overall response rate (ORR) per RECIST v1.1 as assessed by independent review committee (IRC) and duration of response.

There were a total of 171 patients enrolled which included 78 patients enrolled in Cohort A, 57 patients enrolled in Cohort B, and 36 patients enrolled in Cohort C. The characteristics of the study population were a median age of 66 years, 48% male; 81% White, 14% Asian, 3% Black, and 2% Hispanic; 60% were former smokers, 32% were never smokers, and 8% current smokers; 27% had ECOG performance status (PS) 0, 63% had ECOG PS 1, and 11% had ECOG PS of 2; 99% had metastatic disease of which 6% had brain metastasis at baseline and 14% had liver metastasis at baseline; 11% had systemic anti-cancer therapy in the adjuvant setting and 58% of the 135 previously treated patients had only one line of prior systemic therapy for metastatic disease; and 98 % had non-squamous histology.

Efficacy results are summarized in Table 12.

Table 12. Efficacy Results Based on Independent Review in Study BRF113928

Treatment	Dabrafenib	Dabrafenib + Trametinib	
Population	Previously Treated n=78	Previously Treated n=57	Treatment Naïve n=36
Overall Response Rate (95%CI)[a]	27% (18%, 38%)	63% (49%, 76%)	61% (44%, 77%)
Complete response	1%	4%	3%
Partial response	26%	60%	58%
Duration of Response (DOR)	n=21	n=36	n=22
Median DOR, months (95% CI)[a]	9.9 (4.2, NE[b])	12.6 (5.8, NE)	NE (6.9, NE)
% Responders with DOR ≥6 months	52%	64%	59%

[a]CI = Confidence interval
[b] NE=Not estimable

In a subgroup analysis of patients with retrospectively, centrally confirmed BRAF V600E mutation-positive NSCLC with the Oncomine™ Dx Target Test, the ORR results were similar to those presented in Table 12.

16 HOW SUPPLIED/STORAGE AND HANDLING

50 mg capsules: Dark red capsule imprinted with 'GS TEW' and '50 mg' available in bottles of 120 (NDC 0078-0682-66). Each bottle contains a silica gel desiccant.

75 mg capsules: Dark pink capsule imprinted with 'GS LHF' and '75 mg' available in bottles of 120 (NDC 0078-0681-66). Each bottle contains a silica gel desiccant.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Inform patients of the following:

Confirmation of BRAF V600E or V600K mutation

- TAFINLAR as a single agent: Evidence of BRAF V600E mutation in the tumor specimen using an FDA-approved test is necessary to identify patients for whom treatment is indicated *[see Dosage and Administration (2.1)]*.
- TAFINLAR with trametinib: Evidence of BRAF V600 mutation in tumor specimens using an FDA-approved test is necessary to identify patients for whom treatment is indicated *[see Dosage and Administration (2.1)]*.

New cutaneous and non-cutaneous malignancies

TAFINLAR increases the risk of developing new primary cutaneous and non-cutaneous malignancies. Advise patients to contact their healthcare provider immediately for any new lesions, changes to existing lesions on their skin, or signs and symptoms of other malignancies *[see Warnings and Precautions (5.1)]*.

Hemorrhage

TAFINLAR when administered with trametinib increases the risk of intracranial and gastrointestinal hemorrhage. Advise patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual bleeding or hemorrhage *[see Warnings and Precautions (5.3)]*.

Cardiomyopathy

TAFINLAR can cause cardiomyopathy. Advise patients to immediately report any signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Uveitis

TAFINLAR can cause uveitis, including iritis and iridocyclitis. Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.5)]*.

Serious febrile reactions

TAFINLAR can cause pyrexia including serious febrile reactions. Inform patients that the incidence and severity of pyrexia are increased when TAFINLAR is given in combination with trametinib. Instruct patients to contact their healthcare provider if they develop fever while taking TAFINLAR *[see Warnings and Precautions (5.6)]*.

Serious skin toxicities

TAFINLAR can cause serious skin toxicities. Advise patients to contact their healthcare provider for progressive or intolerable rash *[see Warnings and Precautions (5.7)]*.

Hyperglycemia

TAFINLAR can impair glucose control in diabetic patients resulting in the need for more intensive hypoglycemic treatment. Advise patients to contact their healthcare provider to report symptoms of severe hyperglycemia *[see Warnings and Precautions (5.8)]*.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

TAFINLAR may cause hemolytic anemia in patients with G6PD deficiency. Advise patients with known G6PD deficiency to contact their healthcare provider to report signs or symptoms of anemia or hemolysis *[see Warnings and Precautions (5.9)]*.

Embryo-fetal toxicity

TAFINLAR can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the potential risk to a fetus *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1, 8.3)]*.

Females and males of reproductive potential

Instruct females of reproductive potential to use non-hormonal, effective non-hormonal contraception during treatment and for 2 weeks after discontinuation of treatment with TAFINLAR. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1, 8.3)]*.

Infertility

Advise males and females of reproductive potential of the potential risk for impaired fertility with TAFINLAR *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with TAFINLAR and for 2 weeks after the last dose of TAFINLAR *[see Use in Specific Populations (8.2)]*.

Instructions for taking TAFINLAR

Instruct patients to take TAFINLAR at least 1 hour before or at least 2 hours after a meal *[see Dosage and Administration (2.2)]*.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T201X-XX
April 2018

MEDICATION GUIDE
TAFINLAR® (TAFF-in-lar)
(dabrafenib)
capsules

If your healthcare provider prescribes TAFINLAR for you to be taken with trametinib, also read the Patient Information leaflet that comes with trametinib.

What is the most important information I should know about TAFINLAR?

TAFINLAR may cause serious side effects, including the risk of new cancers:

TAFINLAR, when used alone or with trametinib, may cause a type of skin cancer, called cutaneous squamous cell carcinoma (cuSCC). New melanoma lesions may happen in people who take TAFINLAR alone or with trametinib.

TAFINLAR with trametinib, may cause new cancers including basal cell carcinoma.

Talk with your healthcare provider about your risk for these cancers.

Check your skin and tell your healthcare provider right away about any skin changes including a:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

Your healthcare provider should check your skin before treatment with TAFINLAR, every two months during treatment with TAFINLAR, and for up to 6 months after you stop taking TAFINLAR to look for any new skin cancers.

Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that develop during treatment with TAFINLAR.

See "What are the possible side effects of TAFINLAR?" for more information about side effects.

What is TAFINLAR?

TAFINLAR is a prescription medicine used:

- alone or in combination with a medicine called trametinib, to treat people with a type of skin cancer called melanoma that:
  - has spread to other parts of the body or cannot be removed by surgery, **and**
  - that has a certain type of abnormal "BRAF" gene.

TAFINLAR alone or with trametinib should not be used to treat people with a type of skin cancer called wild-type BRAF melanoma.

- TAFINLAR is a prescription medicine used with a medicine called trametinib to treat people with a type of lung cancer called non-small cell lung cancer (NSCLC) that:
  - has spread to other parts of the body (metastatic NSCLC), **and**
  - that has a certain type of abnormal "BRAF" gene.

Your healthcare provider will perform a test to make sure that TAFINLAR is right for you.

It is not known if TAFINLAR alone or TAFINLAR with trametinib is safe and effective in children.

What should I tell my healthcare provider before taking TAFINLAR?
Before you take TAFINLAR, tell your healthcare provider if you:

- have had bleeding problems
- have heart problems
- have eye problems
- have liver or kidney problems
- have diabetes
- plan to have surgery, dental, or other medical procedures
- have a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme
- have any other medical conditions
- are pregnant or plan to become pregnant. TAFINLAR can harm your unborn baby.

- Females who are able to become pregnant should use effective birth control (contraception) during treatment with TAFINLAR, and for 2 weeks after the last dose of TAFINLAR alone, **or** for 4 months after the last dose when taking TAFINLAR with trametinib.
- Birth control methods that contain hormones (such as birth control pills, injections, or patches) may not work as well during treatment with TAFINLAR alone or TAFINLAR and trametinib. You should use another effective method of birth control during treatment with TAFINLAR alone or TAFINLAR and trametinib.
- Talk to your healthcare provider about birth control methods that may be right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with TAFINLAR alone or TAFINLAR and trametinib.

- are breastfeeding or plan to breastfeed. It is not known if TAFINLAR passes into your breast milk.
  - Do not breastfeed during treatment and for 2 weeks after your last dose of TAFINLAR alone, **or** for 4 months after your last dose of TAFINLAR with trametinib. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TAFINLAR and certain other medicines can affect each other, causing side effects. TAFINLAR may affect the way other medicines work, and other medicines may affect how TAFINLAR works. You can ask your pharmacist for a list of medicines that may interact with TAFINLAR.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take TAFINLAR?

- Take TAFINLAR exactly as your healthcare provider tells you. Do not change your dose or stop TAFINLAR unless your healthcare provider tells you.
- Take TAFINLAR 2 times a day, about 12 hours apart.
- Take TAFINLAR at least 1 hour before or 2 hours after a meal.
- Do not open, crush, or break TAFINLAR capsules.
- If you miss a dose of TAFINLAR, take it as soon as you remember. If it is within 6 hours of your next scheduled dose, just take your next dose at your regular time. Do not make up for the missed dose.

What are the possible side effects of TAFINLAR?

TAFINLAR may cause serious side effects, including:

- **See "What is the most important information I should know about TAFINLAR?"**
- TAFINLAR, when taken with trametinib, can cause serious bleeding problems, especially in your brain or stomach, and can lead to death. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
  - headaches, dizziness, or feeling weak
  - cough up blood or blood clots
  - vomit blood or your vomit looks like "coffee grounds"
  - red or black stool that looks like tar
- **heart problems**, including heart failure. Your healthcare provider should check your heart function before and during treatment with TAFINLAR. Call your healthcare provider right away if you have any of the following signs and symptoms of a heart problem:
  - feeling like your heart is pounding or racing
  - shortness of breath
  - swelling of your ankles or feet
  - feeling lightheaded

- **eye problems**. TAFINLAR, when taken alone or with trametinib, can cause severe eye problems that can lead to blindness. Call your healthcare provider right away if you get these symptoms of eye problems:
  - blurred vision, loss of vision, or other vision changes
  - see color dots
  - halo (see blurred outline around objects)
  - eye pain, swelling, or redness
- **fever**. Fever is common during treatment with TAFINLAR alone or with trametinib, but may also be serious. When taking TAFINLAR with trametinib, 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. Call your healthcare provider right away if you get a fever during treatment with TAFINLAR.
- **serious skin reactions**. Rash is a common side effect of TAFINLAR when taken alone, or with trametinib. TAFINLAR, when taken alone or with trametinib, can also cause other skin reactions. In some cases these rashes and other skin reactions can be severe, or serious and may need to be treated in a hospital. Call your healthcare provider if you get any of the following symptoms:
  - skin rash that bothers you or does not go away
  - acne
  - redness, swelling, peeling, or tenderness of hands or feet
  - skin redness
- **increased blood sugar (hyperglycemia)**. Some people may develop high blood sugar or worsening diabetes during treatment with TAFINLAR, alone or with trametinib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with TAFINLAR alone or with trametinib. Your diabetes medicine may need to be changed. Tell your healthcare provider if you 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
- TAFINLAR may cause healthy red blood cells to break down too early in people with G6PD deficiency. This may lead to a type of anemia called hemolytic anemia where the body does not have enough healthy red blood cells. Tell your healthcare provider if you have any of the following signs or symptoms:
  - yellow skin (jaundice)
  - weakness or dizziness
  - shortness of breath

The most common side effects of TAFINLAR alone include:

- thickening of the outer layers of the skin
- headache
- fever
- joint aches
- warts
- hair loss
- redness, swelling, peeling, or tenderness of hands or feet

The most common side effects of TAFINLAR when taken with trametinib in people with melanoma include:

- fever
- rash
- headache
- chills
- joint aches
- cough

The most common side effect of TAFINLAR when taken with trametinib in people with NSCLC include:

- fever
- fatigue
- nausea
- vomiting
- diarrhea
- dry skin
- decreased appetite
- rash
- swelling of face, arms, and legs
- chills
- bleeding
- cough
- shortness of breath

TAFINLAR may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.
TAFINLAR may cause lower sperm counts in males. This could affect the ability to father a child. Talk to your healthcare provider if this is a concern for you.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all of the possible side effects of TAFINLAR. For more information about side effects, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

How should I store TAFINLAR?

- Store TAFINLAR at room temperature between 68°F to 77°F (20°C to 25°C).

Keep TAFINLAR and all medicine out of the reach of children.

General information about the safe and effective use of TAFINLAR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TAFINLAR for a condition for which it was not prescribed. Do not give TAFINLAR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about TAFINLAR that is written for health professionals.

What are the ingredients in TAFINLAR?

Active ingredient: dabrafenib
Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose
Capsule shells: hypromellose, red iron oxide (E172), titanium dioxide (E171).

Distributed by:

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2017