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 (1.2)	01/2014
Dosage and Administration (2.1-2.3)	01/2014
Warnings and Precautions (5-5.9, 5.11)	01/2014

----------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, 2.1)
- TAFINLAR in combination with 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. The use in combination is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib. (1.2, 2.1, 14.2)

Limitation of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma. (1.3, 5.2)

---------- DOSAGE AND ADMINISTRATION ----------

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent. 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)
- The recommended dose of TAFINLAR is 150 mg orally twice daily as a single agent or in combination with trametinib 2 mg orally once 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 in combination with trametinib. Monitor patients for new malignancies prior to initiation of therapy, while on therapy, and following discontinuation of TAFINLAR or the combination therapy. (5.1, 2.3)
- Tumor Promotion in BRAF Wild-Type Melanoma: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Hemorrhage: Major hemorrhagic events can occur in patients receiving TAFINLAR in combination with trametinib. Monitor for signs and symptoms of bleeding. (5.3)
- Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur in patients receiving TAFINLAR in combination with trametinib. (5.4, 2.3)
- Cardiomyopathy: Assess LVEF before treatment with TAFINLAR in combination with trametinib, after one month of treatment, then every 2 to 3 months thereafter. (5.5, 2.3)
- Ocular Toxicities: Perform ophthalmologic evaluation for any visual disturbances. (5.6, 2.3)
- Serious Febrile Reactions: Incidence and severity of pyrexia are increased with TAFINLAR in combination with trametinib. (5.7, 2.3)
- Serious Skin Toxicity: Monitor for skin toxicities and for secondary infections. Discontinue for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of TAFINLAR. (5.8, 2.3)
- Hyperglycemia: Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia. (5.9)
- Glucose-6-Phosphate Dehydrogenase Deficiency: Closely monitor for hemolytic anemia. (5.10)
- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus. TAFINLAR may render hormonal contraceptives less effective and an alternative method of contraception should be used. (5.11, 8.1)

---------- 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 are pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 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)
- Avoid concurrent administration of strong inducers 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 ----------

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Females and Males of Reproductive Potential: Advise female patients to use highly effective contraception during treatment and for 2 weeks following discontinuation of treatment. Advise male patients of potential risk for impaired spermatogenesis. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2014

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® as a single agent is indicated 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, in combination with 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. This indication is based on the demonstration of durable response rate *[see Clinical Studies (14.2)]*. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib.

1.3 Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

2.2 Recommended Dosing

The recommended dosage regimens of TAFINLAR are:

- 150 mg orally taken twice daily, approximately 12 hours apart, as a single agent
- 150 mg orally taken twice daily, approximately 12 hours apart, in combination with trametinib 2 mg orally taken once daily

Continue treatment until disease progression or unacceptable toxicity occurs. Take TAFINLAR as a single agent, or TAFINLAR in combination with trametinib, 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 capsule.

When administered in combination with trametinib, take the once-daily dose of trametinib at the same time each day with either the morning dose or the evening dose of TAFINLAR.

2.3 Dose Modifications

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. If used in combination with trametinib, no dose modifications are required for trametinib in patients who develop non-cutaneous malignancies.

Table 1. Recommended Dose Reductions

Dose Reductions for TAFINLAR When Administered as a Single Agent or in Combination With Trametinib	
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
Dose Reductions for Trametinib When Administered in Combination With TAFINLAR	
First Dose Reduction	1.5 mg orally once daily
Second Dose Reduction	1 mg orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate trametinib 1 mg orally once daily

Table 2. Recommended Dose Modifications for TAFINLAR as a Single Agent and for TAFINLAR and Trametinib Administered in Combination

Severity of Adverse Reaction[a]	TAFINLAR[b]	Trametinib (When Used in Combination)[b,c]
Febrile drug reaction		
• Fever of 101.3°F to 104°F	Withhold TAFINLAR until fever resolves. Then resume at same or lower dose level.	Do not modify the dose of trametinib.
• 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.	Withhold trametinib until fever resolves. Then resume trametinib at same or lower dose level.
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.	Withhold trametinib for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.
Cardiac		
• Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pretreatment value	Do not modify the dose of TAFINLAR.	Withhold trametinib for up to 4 weeks. • If improved to normal LVEF value, resume at a lower dose level. • If not improved to normal LVEF value, permanently discontinue.
• 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.	Permanently discontinue trametinib.

Severity of Adverse Reaction[a]	TAFINLAR[b]	Trametinib (When Used in Combination)[b,c]
Venous Thromboembolism		
• Uncomplicated DVT or PE	Do not modify the dose of TAFINLAR.	Withhold trametinib for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
• Life Threatening PE	Permanently discontinue TAFINLAR.	Permanently discontinue trametinib.
Ocular Toxicities		
• Grade 2-3 retinal pigment epithelial detachments (RPED)	Do not modify the dose of TAFINLAR.	Withhold trametinib for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
• Retinal vein occlusion	Do not modify the dose of TAFINLAR.	Permanently discontinue trametinib.
• Uveitis and Iritis	Withhold TAFINLAR for up to 6 weeks. • If improved to Grade 0-1, then resume at the same dose. • If not improved, permanently discontinue.	Do not modify the dose of trametinib.

Severity of Adverse Reaction[a]	TAFINLAR[b]	Trametinib (When Used in Combination)[b,c]
Pulmonary		
• Interstitial lung disease/pneumonitis	Do not modify the dose of TAFINLAR.	Permanently discontinue trametinib.
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.	Withhold trametinib for up to 3 weeks. • 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.	• Withhold trametinib until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue trametinib.
• Recurrent Grade 4 adverse reaction	Permanently discontinue TAFINLAR.	Permanently discontinue trametinib.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

[b] See Table 1 for recommended dose reductions of TAFINLAR and trametinib.

[c] Refer to Full Prescribing Information for trametinib.

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 prior to initiation of TAFINLAR in combination with trametinib. The following serious adverse reactions of trametinib as a single agent, which may occur when TAFINLAR is used in combination with trametinib, are not described in the Full Prescribing Information for TAFINLAR:

- Retinal vein occlusion
- Interstitial lung disease

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 in combination with trametinib.

Cutaneous Malignancies:

TAFINLAR results in an increased incidence of cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma. TAFINLAR when used in combination with trametinib results in an increased incidence of basal cell carcinoma.

In Trial 1, cutaneous squamous cell carcinomas and keratoacanthomas (cuSCC) occurred in 7% (14/187) of patients treated with TAFINLAR and in none of the patients treated with dacarbazine.

Across clinical trials of TAFINLAR (N = 586), the incidence of cuSCC was 11%. The median time to first cuSCC was 9 weeks (range: 1 to 53 weeks). 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 Trial 1, the incidence of new primary malignant melanomas was 2% (3/187) for patients receiving TAFINLAR while no dacarbazine-treated patient was diagnosed with new primary malignant melanoma.

In Trial 2, the incidence of basal cell carcinoma was increased in patients receiving TAFINLAR in combination with trametinib: 9% (5/55) of patients receiving TAFINLAR in combination with trametinib compared with 2% (1/53) of patients receiving TAFINLAR as a single agent. The range of time to diagnosis of basal cell carcinoma was 28 to 249 days in patients receiving TAFINLAR in combination with trametinib and was 197 days for the patient receiving TAFINLAR as a single agent.

Cutaneous squamous cell carcinoma (SCC), including keratoacanthoma, occurred in 7% of patients receiving TAFINLAR in combination with trametinib and 19% of patients receiving TAFINLAR as a single agent. The range of time to diagnosis of cuSCC was 136 to197 days in the combination arm and was 9 to 197 days in the arm receiving TAFINLAR as a single agent.

New primary melanoma occurred in 2% (1/53) of patients receiving TAFINLAR as a single agent and in none of the 55 patients receiving TAFINLAR in combination with trametinib.

Perform dermatologic evaluations prior to initiation of TAFINLAR as a single agent or in combination with trametinib, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR. No dose modifications of TAFINLAR or trametinib are required in patients who develop new primary cutaneous malignancies.

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 patients receiving TAFINLAR in combination with trametinib four cases of non-cutaneous malignancies were identified: KRAS mutation-positive pancreatic adenocarcinoma (n = 1), recurrent NRAS mutation-positive colorectal carcinoma (n = 1), head and neck carcinoma (n = 1), and glioblastoma (n = 1). Monitor patients receiving the combination closely for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies. If used in combination with trametinib, no dose modification of trametinib is required for patients who develop non-cutaneous malignancies.

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

5.3 Hemorrhage

Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur when TAFINLAR is used in combination with trametinib.

In Trial 2, treatment with TAFINLAR in combination with trametinib resulted in an increased incidence and severity of any hemorrhagic event: 16% (9/55) of patients treated with TAFINLAR in combination with trametinib compared with 2% (1/53) of patients treated with TAFINLAR as a single agent. The major hemorrhagic events of intracranial or gastric hemorrhage occurred in 5% (3/55) of patients treated with TAFINLAR in combination with trametinib compared with none of the 53 patients treated with TAFINLAR as a single agent. Intracranial hemorrhage was fatal in 4% (2/55) of patients receiving TAFINLAR in combination with trametinib.

Permanently discontinue TAFINLAR and trametinib for all Grade 4 hemorrhagic events and for any Grade 3 hemorrhagic events that do not improve. Withhold TAFINLAR for Grade 3

hemorrhagic events; if improved resume at a lower dose level. Withhold trametinib for up to 3 weeks for Grade 3 hemorrhagic events; if improved, resume at a lower dose level.

5.4 Venous Thromboembolism

Venous thromboembolism can occur when TAFINLAR is used in combination with trametinib.

In Trial 2, treatment with TAFINLAR in combination with trametinib resulted in an increased incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE): 7% (4/55) of patients treated with TAFINLAR in combination with trametinib compared with none of the 53 patients treated with TAFINLAR as a single agent. Pulmonary embolism was fatal in 2% (1/55) of patients receiving TAFINLAR in combination with trametinib.

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 TAFINLAR and trametinib for life-threatening PE. Withhold trametinib and continue TAFINLAR at the same dose for uncomplicated DVT or PE; if improved within 3 weeks, trametinib may be resumed at a lower dose level *[see Dosage and Administration (2.3)]*.

5.5 Cardiomyopathy

Cardiomyopathy can occur when TAFINLAR is used in combination with trametinib and with trametinib as a single agent *[refer to Full Prescribing Information for trametinib]*.

In Trial 2, cardiomyopathy occurred in 9% (5/55) of patients treated with TAFINLAR in combination with trametinib and in none of patients treated with TAFINLAR as a single agent. The median time to onset of cardiomyopathy in patients treated with TAFINLAR in combination with trametinib was 86 days (range: 27 to 253 days). Cardiomyopathy was identified within the first month of treatment with TAFINLAR in combination with trametinib in two of five patients. Development of cardiomyopathy resolved in all five patients following dose reduction (4/55) and/or dose interruption (1/55).

Across clinical trials of TAFINLAR administered in combination with trametinib (N = 202), 8% of patients developed evidence of cardiomyopathy (decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF ≥10% below baseline). Two percent demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of ≥20% below baseline.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of TAFINLAR in combination with trametinib, one month after initiation, and then at 2- to 3-month intervals while on treatment with the combination. Withhold treatment with trametinib and continue TAFINLAR at the same dose if absolute LVEF value decreases by 10% from pretreatment values and is less than the lower limit of normal. For symptomatic cardiomyopathy or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue trametinib and withhold TAFINLAR. Resume TAFINLAR at the same dose level upon recovery of cardiac function *[see Dosage and Administration (2.3)]*.

5.6 Ocular Toxicities

Retinal Pigment Epithelial Detachment (RPED):

Retinal pigment epithelial detachments (RPED) can occur when TAFINLAR is used in combination with trametinib and with trametinib as a single agent *[refer to Full Prescribing Information for trametinib]*. Retinal detachments resulting from trametinib are often bilateral and multifocal, occurring in the macular region of the retina.

In Trial 2, ophthalmologic examinations including retinal evaluation were performed pretreatment and at regular intervals during treatment. RPED occurred in 2% (1/55) of patients receiving TAFINLAR in combination with trametinib. Across clinical trials of TAFINLAR administered in combination with trametinib (N = 202), the incidence of RPED was 1% (2/202).

Perform ophthalmological evaluation at any time a patient reports visual disturbances and compare with baseline, if available. If TAFINLAR is used in combination with trametinib, do not modify the dose of TAFINLAR. Withhold trametinib if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmological evaluation within 3 weeks, resume trametinib at a lower dose level. Discontinue trametinib if no improvement after 3 weeks *[see Dosage and Administration (2.3)]*.

Uveitis and Iritis:

Uveitis and iritis can occur when TAFINLAR is administered as a single agent or when used in combination with trametinib.

Uveitis (including iritis) occurred in 1% (6/586) of patients treated with TAFINLAR as a single agent and uveitis occurred in 1% (2/202) of patients treated with TAFINLAR in combination with trametinib. Symptomatic 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 diagnosed, withhold TAFINLAR for up to 6 weeks until uveitis/iritis resolves to Grade 0-1. If TAFINLAR is used in combination with trametinib, do not modify the dose of trametinib.

5.7 Serious Febrile Reactions

Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur when TAFINLAR is administered as a single agent or when used in combination with trametinib. The incidence and severity of pyrexia are increased when TAFINLAR is used in combination with trametinib compared with TAFINLAR as a single agent *[see Adverse Reactions (6.1)]*.

In Trial 1, the incidence of fever (serious and non-serious) was 28% in patients treated with TAFINLAR and 10% in patients treated with dacarbazine. In patients treated with TAFINLAR, the median time to initial onset of fever (any severity) was 11 days (range: 1 to 202 days) and the median duration of fever was 3 days (range: 1 to 129 days). Serious febrile reactions and fever of

any severity complicated by hypotension, rigors or chills occurred in 3.7% (7/187) of patients treated with TAFINLAR and in none of the 59 patients treated with dacarbazine.

In Trial 2, the incidence of fever (serious and non-serious) was 71% (39/55) in patients treated with TAFINLAR in combination with trametinib and 26% (14/53) in patients treated with TAFINLAR as a single agent. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills occurred in 25% (14/55) of patients treated with TAFINLAR in combination with trametinib compared with 2% (1/53) of patients treated with TAFINLAR as a single agent. Fever was complicated with chills/rigors in 51% (28/55), dehydration in 9% (5/55), renal failure in 4% (2/55), and syncope in 4% (2/55) of patients in Trial 2.

In patients treated with TAFINLAR in combination with trametinib, the median time to initial onset of fever was 30 days compared with 19 days in patients treated with TAFINLAR as a single agent; the median duration of fever was 6 days with the combination compared with 4 days with TAFINLAR as a single agent.

Across clinical trials of TAFINLAR administered in combination with trametinib (N = 202), the incidence of pyrexia was 57% (116/202).

Withhold TAFINLAR for fever of 101.3ºF or higher. Withhold trametinib for any fever higher than 104ºF. Withhold TAFINLAR, and trametinib if used in combination, 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. Refer to Table 2 for recommended dose modifications for adverse reactions *[see Dosage and Administration (2.3)]*. Prophylaxis with antipyretics may be required when resuming TAFINLAR or trametinib.

5.8 Serious Skin Toxicity

Serious skin toxicity can occur when TAFINLAR is used in combination with trametinib and with trametinib as a single agent *[refer to Full Prescribing Information for trametinib]*.

In Trial 2, the incidence of any skin toxicity was similar for patients receiving TAFINLAR in combination with trametinib (65% [36/55]) compared with patients receiving TAFINLAR as a single agent (68% [36/53]). The median time to onset of skin toxicity in patients treated with TAFINLAR in combination with trametinib was 37 days (range: 1 to 225 days) and median time to resolution of skin toxicity was 33 days (range: 3 to 421 days). No patient required dose reduction or permanent discontinuation of TAFINLAR or trametinib for skin toxicity.

Across clinical trials of TAFINLAR in combination with trametinib (N = 202), severe skin toxicity and secondary infections of the skin requiring hospitalization occurred in 2.5% (5/202) of patients treated with TAFINLAR in combination with trametinib.

Withhold TAFINLAR, and trametinib if used in combination, for intolerable or severe skin toxicity. TAFINLAR and trametinib may be resumed at lower dose levels in patients with improvement or recovery from skin toxicity within 3 weeks *[see Dosage and Administration (2.3)]*.

5.9 Hyperglycemia

Hyperglycemia can occur when TAFINLAR is administered as a single agent or when used in combination with trametinib.

In Trial 1, 5 of 12 patients with a history of diabetes required more intensive hypoglycemic therapy while taking TAFINLAR. The incidence of Grade 3 hyperglycemia based on laboratory values was 6% (12/187) in patients treated with TAFINLAR compared with none of the dacarbazine-treated patients.

In Trial 2, the incidence of Grade 3 hyperglycemia based on laboratory values was 5% (3/55) in patients treated with TAFINLAR in combination with trametinib compared with 2% (1/53) in patients treated with TAFINLAR as a single agent.

Monitor serum glucose levels as clinically appropriate when TAFINLAR is administered as a single agent or when used in combination with trametinib in patients with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

5.10 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.

5.11 Embryofetal Toxicity

Based on 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 this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Advise female patients of reproductive potential to use a highly effective non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective, during treatment and for at least 2 weeks after treatment with TAFINLAR or for 4 months after treatment with TAFINLAR in combination with trametinib. 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 (8.6)]*.

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)]*
- Venous Thromboembolism *[see Warnings and Precautions (5.4)]*
- Cardiomyopathy *[see Warnings and Precautions (5.5)]*
- Ocular Toxicities *[see Warnings and Precautions (5.6)]*
- Serious Febrile Reactions *[see Warnings and Precautions (5.7)]*
- Serious Skin Toxicity *[see Warnings and Precautions (5.8)]*
- Hyperglycemia *[see Warnings and Precautions (5.9)]*
- Glucose-6-Phosphate Dehydrogenase Deficiency *[see Warnings and Precautions (5.10)]*

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 and below reflect exposure to TAFINLAR as a single agent and in combination with trametinib.

BRAF V600E Unresectable or Metastatic Melanoma:

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).

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of Trial 1 *[see Clinical Studies (14.1)]*. Trial 1, 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 ≥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 Trial 1 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. Selected Common Adverse Reactions Occurring in ≥10% (All Grades) or ≥2% (Grades 3 or 4) of Patients Treated With TAFINLAR[a]

Primary System Organ Class Preferred Term	TAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and subcutaneous tissue disorders				
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 disorders				
Headache	32	0	8	0
General disorders and administration site conditions				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue disorders				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)				
Papilloma[c]	27	0	2	0
cuSCC[d, e]	7	4	0	0
Respiratory, thoracic, and mediastinal disorders				
Cough	12	0	5	0
Gastrointestinal disorders				
Constipation	11	2	14	0
Infections and infestations				
Nasopharyngitis	10	0	3	0

[a] Adverse drug reactions, reported using MedDRA and graded using 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] Includes squamous cell carcinoma of the skin and keratoacanthoma.

[e] Cases of cutaneous squamous cell carcinoma 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 Trial 1 [Between-Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3 or 4)]

	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[a]	14	2
Increased alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

[a] Grade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

Other clinically important adverse reactions observed in <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.

BRAF V600E or V600K Unresectable or Metastatic Melanoma:

The safety of TAFINLAR in combination with trametinib was evaluated in Trial 2 and other trials consisting of a total of 202 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received TAFINLAR 150 mg orally twice daily in combination with trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. Among these 202 patients, 66 (33%) were exposed to TAFINLAR and 68 (34%) were exposed to trametinib for greater than 6 to 12 months while 40 (20%) were exposed to TAFINLAR and 36 (18%) were exposed to trametinib for greater than one year. The median age was 54 years, 57% were male, and >99% were white.

Table 5 presents adverse reactions from Trial 2, a multicenter, open-label, randomized trial of 162 patients with BRAF V600E or V600K mutation-positive melanoma receiving TAFINLAR 150 mg twice daily in combination with trametinib 2 mg orally once daily (n = 55), TAFINLAR 150 mg orally twice daily in combination with trametinib 1 mg once daily (n = 54), and TAFINLAR as a single agent 150 mg orally twice daily (n = 53) *[see Clinical Studies (14.2)]*. Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, current evidence of Class II or greater congestive heart failure (New York Heart Association), history RVO or RPED, QTc interval ≥480 msec, treatment refractory hypertension, uncontrolled arrhythmias, history of pneumonitis or interstitial lung disease, or a known history of G6PD deficiency were excluded. The median duration of treatment was 10.9 months for both

TAFINLAR and trametinib (2-mg orally once-daily treatment group) when used in combination, 10.6 months for both TAFINLAR and trametinib (1-mg orally once-daily treatment group) when used in combination, and 6.1 months for TAFINLAR as a single agent.

In Trial 2, 13% of patients receiving TAFINLAR in combination with trametinib experienced adverse reactions resulting in permanent discontinuation of trial medication(s). The most common adverse reaction resulting in permanent discontinuation was pyrexia (4%). Adverse reactions led to dose reductions in 49% and dose interruptions in 67% of patients treated with TAFINLAR in combination with trametinib. Pyrexia, chills, and nausea were the most common reasons cited for dose reductions and pyrexia, chills, and decreased ejection fraction were the most common reasons cited for dose interruptions of TAFINLAR and trametinib when used in combination.

Table 5. Common Adverse Drug Reactions Occurring in ≥10% at (All Grades) or ≥5% (Grades 3 or 4) of Patients Treated With TAFINLAR in Combination With Trametinib in Trial 2

	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
Adverse Reactions	**All Grades[a]**	**Grades 3 and 4**	**All Grades[a]**	**Grades 3 and 4**	**All Grades[a]**	**Grades 3 and 4**
General disorders and administrative site conditions						
Pyrexia	71	5	69	9	26	0
Chills	58	2	50	2	17	0
Fatigue	53	4	57	2	40	6
Edema peripheral[b]	31	0	28	0	17	0
Skin and subcutaneous tissue disorders						
Rash[c]	45	0	43	2	53	0
Night Sweats	24	0	15	0	6	0
Dry skin	18	0	9	0	6	0
Dermatitis acneiform	16	0	11	0	4	0
Actinic keratosis	15	0	7	0	9	0
Erythema	15	0	6	0	2	0
Pruritus	11	0	11	0	13	0
Gastrointestinal disorders						
Nausea	44	2	46	6	21	0
Vomiting	40	2	43	4	15	0
Diarrhea	36	2	26	0	28	0
Abdominal pain[d]	33	2	24	2	21	2
Constipation	22	0	17	2	11	0
Dry mouth	11	0	11	0	6	0
Nervous system disorders						
Headache	29	0	37	2	28	0
Dizziness	16	0	13	0	9	0
Respiratory, thoracic, and mediastinal disorders						
Cough	29	0	11	0	21	0
Oropharyngeal pain	13	0	7	0	0	0

Adverse Reactions	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
Musculoskeletal, connective tissue, and bone disorders						
Arthralgia	27	0	44	0	34	0
Myalgia	22	2	24	0	23	2
Back pain	18	5	11	0	11	2
Muscle spasms	16	0	2	0	4	0
Pain in extremity	16	0	11	2	19	0
Metabolism and nutritional disorders						
Decreased appetite	22	0	30	0	19	0
Dehydration	11	0	6	2	2	0
Psychiatric Disorders						
Insomnia	18	0	11	0	8	2
Vascular disorders						
Hemorrhage[e]	16	5	11	0	2	0
Infections and infestations						
Urinary tract infection	13	2	6	0	9	2
Renal and urinary disorders						
Renal failure[f]	7	7	2	0	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

[b] Includes the following terms: peripheral edema, edema, and lymphedema.

[c] Includes the following terms: rash, rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, and rash maculo-papular.

[d] Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

[e] Includes the following terms: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage.

[f] Includes the following terms: renal failure and renal failure acute.

Other clinically important adverse reactions (N = 202) observed in <10% of patients treated with TAFINLAR in combination with trametinib were:

Eye Disorders: Vision blurred, transient blindness.

Gastrointestinal Disorders: Stomatitis, pancreatitis.

General Disorders and Administration Site Conditions: Asthenia.

Infections and Infestations: Cellulitis, folliculitis, paronychia, rash pustular.

Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps): Skin papilloma.

Skin and Subcutaneous Tissue Disorders: Palmar-plantar erythrodysesthesia syndrome, hyperkeratosis, hyperhidrosis.

Vascular Disorders: Hypertension.

Table 6. Treatment-Emergent Laboratory Abnormalities Occurring at ≥10% (All Grades) or ≥2% (Grades 3 or 4)] of Patients Treated With TAFINLAR in Combination With Trametinib in Trial 2

	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
Tests	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4[a]**
Hematology						
Leukopenia	62	5	46	4	21	0
Lymphopenia	55	22	59	19	40	6
Neutropenia	55	13	37	2	9	2
Anemia	55	4	46	7	28	0
Thrombocytopenia	31	4	31	2	8	0
Liver Function Tests						
Increased AST	60	5	54	0	15	0
Increased alkaline phosphatase	60	2	67	6	26	2
Increased ALT	42	4	35	4	11	0
Hyperbilirubinemia	15	0	7	4	0	0
Chemistry						
Hyperglycemia	58	5	67	6	49	2
Increased GGT	56	11	54	17	38	2
Hyponatremia	55	11	48	15	36	2
Hypoalbuminemia	53	0	43	2	23	0
Hypophosphatemia	47	5	41	11	40	0
Hypokalemia	29	2	15	2	23	6
Increased creatinine	24	5	20	2	9	0
Hypomagnesemia	18	2	2	0	6	0
Hyperkalemia	18	0	22	0	15	4
Hypercalcemia	15	0	19	2	4	0
Hypocalcemia	13	0	20	0	9	0

[a] No Grade 4 events were reported in patients receiving TAFINLAR as a single agent.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyltransferase.

QT Prolongation: In Trial 2, QTcF prolongation to >500 msec occurred in 4% (2/55) of patients treated with TAFINLAR in combination with trametinib and in 2% (1/53) of patients treated with TAFINLAR as a single agent. The QTcF was increased more than 60 msec from baseline in 13% (7/55) of patients treated with TAFINLAR in combination with trametinib and 2% (1/53) of patients treated with TAFINLAR as a single agent.

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 and strong inducers of CYP3A4 or CYP2C8 may decrease concentrations of dabrafenib *[see Clinical Pharmacology (12.3)]*. Substitution of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, gemfibrozil) or strong inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors or loss of efficacy when taking strong inducers.

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, 8.6)]*. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

7.3 Trametinib

Coadministration of TAFINLAR 150 mg twice daily and trametinib 2 mg once daily resulted in no clinically relevant pharmacokinetic drug interactions *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D.

Risk Summary: Based on 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 of 150 mg twice daily based on AUC. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Warnings and Precautions (5.11)]*.

Animal Data: In a combined female fertility and embryofetal development study in rats, 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.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions from TAFINLAR in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TAFINLAR have not been established in pediatric patients.
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 Trial 1 were ≥65 years of age. No overall differences in the effectiveness or safety of TAFINLAR were observed in the elderly in Trial 1.

Across all clinical trials of TAFINLAR administered in combination with trametinib, there was an insufficient number of patients aged 65 years and over to determine whether they respond differently from younger patients. In Trial 2, 11 patients (20%) were 65 years of age and older, and 2 patients (4%) were 75 years of age and older.

8.6 Females and Males of Reproductive Potential

Contraception: *Females:* Advise female patients of reproductive potential to use highly effective contraception during treatment and for at least 2 weeks after the last dose of TAFINLAR or at least 4 months after the last dose of TAFINLAR taken in combination with trametinib. Counsel patients to use a non-hormonal method of contraception since TAFINLAR

can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Warnings and Precautions (5.11), Drug Interactions (7.1), Use in Specific Populations (8.1)]*.

Infertility:

Females: Increased follicular cysts and decreased corpora lutea were observed in female rats treated with trametinib. Advise female patients of reproductive potential that TAFINLAR taken in combination with trametinib may impair fertility in female patients.

Males: Effects on spermatogenesis have been observed in animals. Advise male patients of the potential risk for impaired spermatogenesis, and to seek counseling on fertility and family planning options prior to starting treatment with TAFINLAR *[see Nonclinical Toxicology (13.1)]*.

8.7 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)]*.

8.8 Renal Impairment

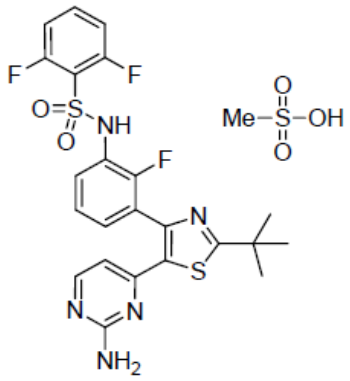
No formal pharmacokinetic trial in patients with renal impairment has been conducted. Dose adjustment is not recommended for patients with mild or moderate renal impairment based on the results of the population pharmacokinetic analysis. An appropriate dose has not been established for patients with 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 BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo.

Dabrafenib and trametinib target two different tyrosine 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 melanoma cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive melanoma xenografts compared with either drug alone.

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. Hydroxy-dabrafenib terminal half-life (10 hours) parallels that of dabrafenib while the carboxy- and desmethyl-dabrafenib metabolites exhibited longer half-lives (21 to 22 hours). 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. 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: 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: 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:

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. Dabrafenib is a substrate of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro.

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 dabrafenib 150 mg twice daily for 15 days and a single dose of midazolam 3 mg (a CYP3A4 substrate) decreased midazolam AUC by 74%. 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% *[see Drug Interactions (7.2)]*.

Dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib, are inhibitors of human organic anion transporting polypeptide OATP1B1, OATP1B3 and organic anion transporter OAT1 and OAT3 in vitro. Dabrafenib and desmethyl-dabrafenib are inhibitors of BCRP in vitro.

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 trametinib or hydroxy-dabrafenib as compared with administration of either drug alone.

Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of dabrafenib. When TAFINLAR is coadministered with a proton pump inhibitor, H_2-receptor antagonist, or antacid, systemic exposure of dabrafenib may be decreased and the effect on efficacy of TAFINLAR is unknown.

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 embryofetal 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

In Trial 1, 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 Trial 1 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.

Trial 1 demonstrated a statistically significant increase in progression-free survival in the patients treated with TAFINLAR. Table 7 and Figure 1 summarize the PFS results.

Table 7. Investigator-Assessed Progression-Free Survival and Confirmed Objective Response Results in Trial 1

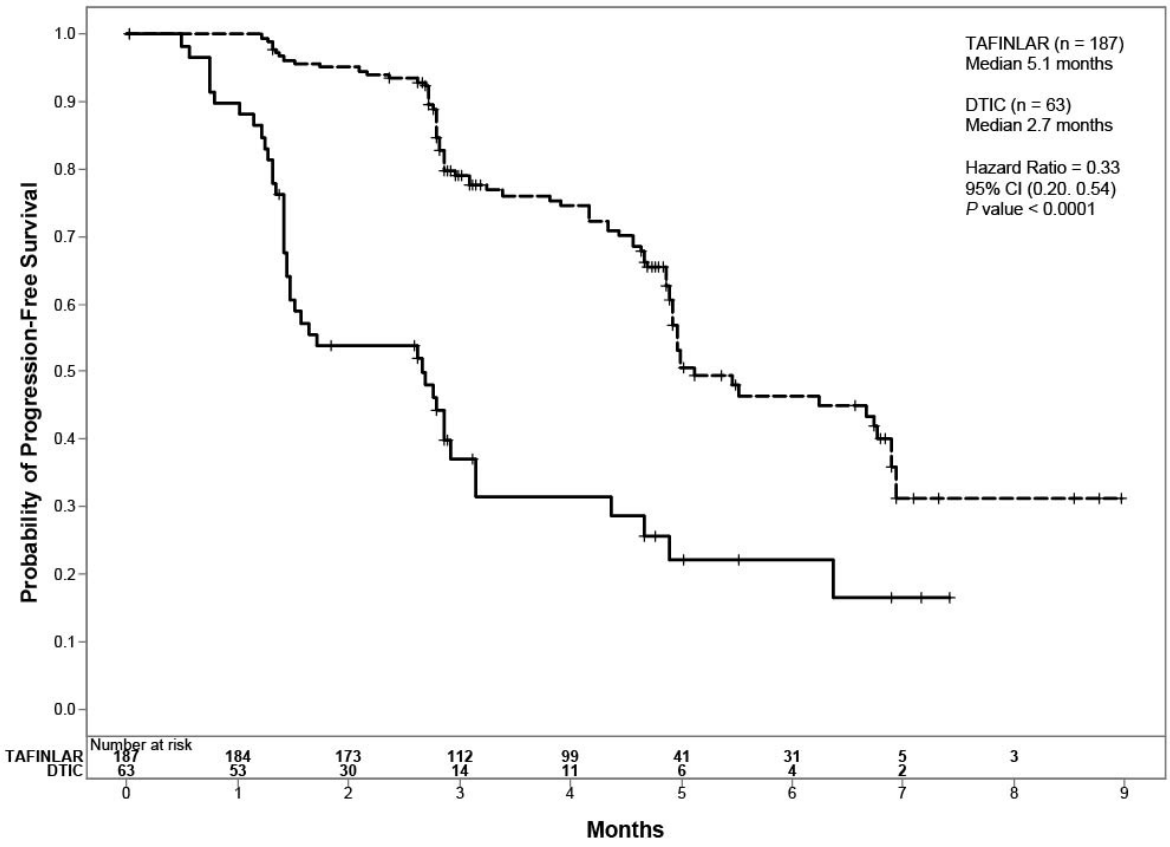
	TAFINLAR N = 187	**Dacarbazine N = 63**
Progression-free Survival		
Number of Events (%)	78 (42%)	41 (65%)
Progressive Disease	76	41
Death	2	0
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR[a] (95% CI)	0.33 (0.20, 0.54)	
P-value[b]	*P* <0.0001	
Confirmed Tumor Responses		
Objective Response 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)

[a] Pike estimator, stratified by disease state.

[b] Stratified log-rank test.

CI = Confidence interval; CR = Complete response; HR = Hazard ratio; NR = Not reached; PR = Partial response.

Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival



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 multi-center trial (Trial 3). 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, charged particles, or CyberKnife. 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 8.

Table 8. Efficacy Results in Patients With BRAF V600E Melanoma Brain Metastases (Trial 3)

	IRRC Assessed Response	
Endpoint	**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 Median, months (95% CI)	(N = 13) 4.6 (2.8, NR)	(N = 12) 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

Trial 2 was a multicenter, open-label, randomized (1:1:1) dose-ranging trial designed to evaluate the clinical activity and safety of TAFINLAR in combination with trametinib (at two different doses) and to compare the safety with TAFINLAR as a single agent in 162 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. Patients were permitted to have had one prior chemotherapy regimen and prior aldesleukin; patients with prior exposure to BRAF or MEK inhibitors were ineligible. Patients were randomized to receive TAFINLAR 150 mg orally twice daily with trametinib 2 mg orally once daily (n = 54), TAFINLAR 150 mg orally twice daily with trametinib 1 mg orally twice daily (n = 54), or TAFINLAR 150 mg orally twice daily (n = 54). Treatment continued until disease progression or unacceptable toxicity. Patients randomized to TAFINLAR as a single agent were offered TAFINLAR 150 mg orally twice daily with trametinib 2 mg orally once daily at the time of investigator-assessed disease progression. The major efficacy outcome measure was investigator-assessed overall response rate (ORR). Additional efficacy outcome measures were investigator-assessed duration of response, independent radiology review committee (IRRC)-assessed ORR, and IRRC-assessed duration of response.

The median age of patients was 53 years, 57% were male, >99% were white, 66% of patients had a pre-treatment ECOG performance status of 0, 67% had M1c disease, 54% had a normal LDH at baseline, and 8% had history of brain metastases. Most patients (81%) had not received prior anti-cancer therapy for unresectable or metastatic disease. Based on local laboratory or centralized testing, 85% of patients' tumors had BRAF V600E mutations and 15% had BRAF V600K mutations.

The median duration of follow-up was 14 months. Efficacy outcomes for the trial arms receiving TAFINLAR in combination with trametinib 2 mg orally once daily and TAFINLAR as a single agent, are summarized in Table 9.

Table 9. Investigator-Assessed and Independent Review Committee-Assessed Response Rates and Response Duration in Trial 2

Endpoints	TAFINLAR plus Trametinib N = 54	TAFINLAR N = 54
Investigator Assessment		
Responders (ORR%) (95% CI)	41 (76%) (62%, 87%)	29 (54%) (40%, 67%)
Complete response	9%	4%
Partial response	67%	50%
Duration of Response (months)		
Median (95% CI)	10.5 (7, 15)	5.6 (5, 7)
Independent Radiology Review Committee Assessment		
Responders (ORR%) (95% CI)	31 (57%) (43%, 71%)	25 (46%) (33%, 60%)
Complete response	9%	7%
Partial response	48%	39%
Duration of Response (months)		
Median (95% CI)	7.6 (7, NR)	7.6 (6, NR)

CI = Confidence interval; ORR = Confirmed overall response rate; NR = Not reported.

The ORR results were similar in subgroups defined by BRAF mutation subtype, i.e., in the 85% of patients with V600E mutation-positive melanoma and in the 15% of patients with V600K mutation-positive melanoma. In exploratory subgroup analyses of the patients with retrospectively confirmed BRAF V600E or V600K mutation-positive melanoma using the THxID™-BRAF assay, the ORR results were also similar to the intent-to-treat analysis.

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 0173-0846-08). 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 0173-0847-08). Each bottle contains a silica gel desiccant.

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Inform patients of the following:

- Evidence of BRAF V600E mutation in the tumor specimen is necessary to identify patients for whom treatment with TAFINLAR as a single agent is indicated and evidence of BRAF V600E or V600K mutation in tumor specimens is necessary to identify patients for whom treatment with TAFINLAR in combination with trametinib is indicated *[see Dosage and Administration (2.1)]*.
- TAFINLAR increases the risk of developing new primary cutaneous and non-cutaneous malignancies. Advise patients to contact their doctor 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)]*.
- TAFINLAR administered in combination 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)]*.
- TAFINLAR administered in combination with trametinib increases the risks of pulmonary embolism and deep venous thrombosis. Advise patients to seek immediate medical attention for sudden onset of difficulty breathing, leg pain, or swelling *[see Warnings and Precautions (5.4)]*.
- TAFINLAR administered in combination with trametinib can cause cardiomyopathy. Advise patients to immediately report any signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.5)]*.
- TAFINLAR can cause visual disturbances; TAFINLAR administered in combination with trametinib can lead to blindness. Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.6)]*.
- TAFINLAR, administered as a single agent and in combination with trametinib 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 doctor if they develop fever while taking TAFINLAR *[see Warnings and Precautions (5.7)]*.

- TAFINLAR in combination with trametinib can cause serious skin toxicities which may require hospitalization. Advise patients to contact their healthcare provider for progressive or intolerable rash *[see Warnings and Precautions (5.8)]*.
- TAFINLAR can impair glucose control in diabetic patients resulting in the need for more intensive hypoglycemic treatment. Advise patients to contact their doctor to report symptoms of severe hyperglycemia *[see Warnings and Precautions (5.9)]*.
- TAFINLAR may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Advise patients with known G6PD deficiency to contact their doctor to report signs or symptoms of anemia or hemolysis *[see Warnings and Precautions (5.10)]*.
- TAFINLAR can cause fetal harm if taken during pregnancy. Instruct female patients to use non-hormonal, highly effective contraception during treatment and for 2 weeks after discontinuation of treatment with TAFINLAR as a single agent, or for 4 months after discontinuation of treatment with TAFINLAR in combination with trametinib. Advise patients to contact their doctor if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.
- Nursing infants may experience serious adverse reactions if the mother is taking TAFINLAR during breastfeeding. Advise breastfeeding mothers to discontinue nursing while taking TAFINLAR *[see Use in Specific Populations (8.3)]*.
- Male patients are at an increased risk for impaired spermatogenesis *[see Use in Specific Populations (8.6)]*.
- TAFINLAR should be taken either at least 1 hour before or at least 2 hours after a meal *[see Dosage and Administration (2.1)]*.

GlaxoSmithKline
Research Triangle Park, NC 27709

TFR:XPI

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

If your healthcare provider prescribes TAFINLAR for you in combination 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 in combination with trametinib, may cause a type of skin cancer, called cutaneous squamous cell carcinoma (cuSCC). New melanoma lesions have also occurred in people who take TAFINLAR.**
- **TAFINLAR, in combination 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 you start taking TAFINLAR, and every two months while taking TAFINLAR, to look for any new skin cancers. Your healthcare provider may continue to check your skin for six months after you stop taking TAFINLAR.

Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that have developed while taking TAFINLAR in combination with trametinib.

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 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.

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

TAFINLAR (alone or in combination with trametinib) is not used to treat people with a type of skin cancer called wild-type BRAF melanoma.

It is not known if TAFINLAR 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 or blood clots
- 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 birth control (contraception) during treatment with TAFINLAR and for 2 weeks after stopping treatment with TAFINLAR alone, or for 4 months when taking TAFINLAR in combination with trametinib.
    - Birth control using hormones (such as birth control pills, injections, or patches) may not work as well while you are taking TAFINLAR alone or in combination with trametinib. You should use another effective method of birth control while taking TAFINLAR alone or in combination with 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 during treatment with TAFINLAR alone or in combination with trametinib.
- are breastfeeding or plan to breastfeed. It is not known if TAFINLAR passes into your breast milk. You and your healthcare provider should decide if you will take TAFINLAR or breastfeed. You should not do both.

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.
- If you take TAFINLAR in combination with trametinib, take the first dose of TAFINLAR in the morning, and take the second dose of TAFINLAR in the evening, about 12 hours apart. Take trametinib 1 time a day at the same time each day, either with the morning or the evening dose of TAFINLAR.
- 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. But, 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.
- If you are taking TAFINLAR in combination with trametinib and you miss a dose of trametinib, take it as soon as you remember. But, if it is within 12 hours of your next scheduled dose of trametinib, just take your next dose at your regular time. Do not make up for the missed dose.
- If you take too much TAFINLAR, call your healthcare provider or go to the nearest hospital emergency room right away.

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?”**
- **bleeding problems.** TAFINLAR, in combination 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 unusual 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 stools that look like tar

- **blood clots.** TAFINLAR, in combination with trametinib, can cause blood clots in your arms or legs, which can travel to your lungs and can lead to death. Get medical help right away if you have the following symptoms:
  - chest pain
  - sudden shortness of breath or trouble breathing
  - pain in your legs with or without swelling
  - swelling in your arms or legs
  - a cool or pale arm or leg
- **heart problems, including heart failure.** Your healthcare provider should check your heart function before you start taking TAFINLAR in combination with trametinib and during treatment. 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 and feet
  - feeling lightheaded
- **eye problems.** TAFINLAR alone, or in combination 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 (seeing blurred outline around objects)
  - eye pain, swelling, or redness
- **fever.** TAFINLAR alone or in combination with trametinib can cause fever which may be serious. When taking TAFINLAR, in combination 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 while taking TAFINLAR.

- **skin reactions.** Rash is a common side effect of TAFINLAR alone, or when used in combination with trametinib. TAFINLAR alone, or in combination with trametinib, can also cause other skin reactions. In some cases these rashes and other skin reactions can be severe, 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 in combination with trametinib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with TAFINLAR alone or in combination 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 of anemia or breakdown of red blood cells:
  - yellow skin (jaundice)
  - weakness or dizziness
  - shortness of breath

The most common side effects of TAFINLAR when used alone include:

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

Common side effects of TAFINLAR when used in combination with trametinib include:

- tiredness
- nausea or vomiting
- stomach-area (abdominal) pain
- diarrhea
- cough
- swelling of the face, arms, or legs
- headache
- night sweats
- decreased appetite
- constipation
- muscle or joint aches

TAFINLAR, in combination with trametinib, 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 GlaxoSmithKline at 1-888-825-5249.

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 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.

For more information, call GlaxoSmithKline at 1-888-825-5249 or go to www.TAFINLAR.com.

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).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline

Research Triangle Park, NC 27709

Revised: January 2014

TFR:XMG