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

INDICATIONS AND USAGE

TAFINLAR is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1, 2.1)

Limitation of use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma. (1, 5.2)

DOSAGE AND ADMINISTRATION

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR. (2.1)
- The recommended dose is 150 mg orally twice daily taken 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 Cutaneous Malignancies: Perform dermatologic evaluations prior to initiation of therapy, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR. (5.1)
- Tumor Promotion in BRAF Wild-Type Melanoma: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Serious Febrile Drug Reactions: Withhold TAFINLAR if fever ≥101.3°F or complicated fever occurs. (5.3)
- Hyperglycemia: Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia. (5.4)
- Uveitis and Iritis: Monitor patients routinely for visual symptoms. (5.5)
- Glucose-6-Phosphate Dehydrogenase Deficiency: Closely monitor for hemolytic anemia. (5.6)
- 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. (5.7, 8.1)

ADVERSE REACTIONS

Most common adverse reactions (≥20%) for TAFINLAR are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. (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

- Concurrent administration of strong inhibitors of CYP3A4 or CYP2C8 is not recommended. (7.1)
- Concurrent administration of strong inducers of CYP3A4 or CYP2C8 is not recommended. (7.1)
- Drugs that increase gastric pH may decrease dabrafenib concentrations. (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 4 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: 12/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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 *[see Warnings and Precautions (5.2)]*. 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 dose for TAFINLAR is 150 mg orally taken twice daily, approximately 12 hours apart, until disease progression or unacceptable toxicity occurs. Take either at least 1 hour before or at least 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.

A missed dose can be taken up to 6 hours prior to the next dose. Do not open, crush, or break TAFINLAR capsule.

2.3 Dose Modifications

For New Primary Cutaneous Malignancies: No dose modifications are recommended.

22 **Table 1. Recommended Dose Modifications for TAFINLAR**

Target Organ	Adverse Reactions[a]	Dose Modification
Febrile Drug Reaction	• Fever of 101.3ºF to 104°F	Withhold TAFINLAR until adverse reaction resolves. Then resume TAFINLAR at same dose or at a reduced dose level (see Table 2).
	• Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure	Either • Permanently discontinue TAFINLAR Or • Withhold TAFINLAR until adverse reaction resolves. Then resume TAFINLAR at a reduced dose level (see Table 2).
Other	• Intolerable Grade 2 Adverse Reactions • Any Grade 3 Adverse Reactions	Withhold TAFINLAR until adverse reaction resolves to Grade 1 or less. Then resume TAFINLAR at a reduced dose level (see Table 2).
	• First occurrence of Any Grade 4 Adverse Reaction	Either • Permanently discontinue TAFINLAR Or • Withhold TAFINLAR until adverse reaction resolves to Grade 1 or less. Then resume TAFINLAR at a reduced dose level (see Table 2).
	• Recurrent Grade 4 Adverse Reaction • Intolerable Grade 2 or Any Grade 3 or 4 Adverse Reaction on TAFINLAR 50 mg twice daily	Permanently discontinue TAFINLAR.

23 [a] Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 2. Recommended Dose Reductions for TAFINLAR

Dose Reductions	Dose and Schedule
First dose reduction	100 mg orally twice daily
Second dose reduction	75 mg orally twice daily
Third dose reduction	50 mg orally twice daily
If unable to tolerate 50 mg twice daily	Discontinue 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

5.1 New Primary Cutaneous Malignancies

TAFINLAR results in an increased incidence of cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma. 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 a cuSCC, approximately 33% developed one or more cuSCC with continued 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 chemotherapy-treated patient was diagnosed with new primary malignant melanoma.

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

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 mutation status prior to initiation of TAFINLAR *[see Indications and Usage (1) and Dosage and Administration (2.1)]*.

5.3 Serious Febrile Drug Reactions

In Trial 1, serious febrile drug reactions, defined as serious cases of fever or fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure in the absence of another identifiable cause (e.g., infection) occurred in 3.7% (7/187) of patients treated with TAFINLAR and in none of the patients treated with dacarbazine. 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).

Withhold TAFINLAR for fever of 101.3ºF or greater or for any serious febrile drug reaction and evaluate for signs and symptoms of infection. Refer to Table 1 for recommended dose modifications for adverse reactions *[see Dosage and Administration (2.3)]*. Prophylaxis with antipyretics may be required when resuming TAFINLAR.

5.4 Hyperglycemia

Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycemic agent therapy can occur with TAFINLAR. In Trial 1, five 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 to none of the dacarbazine-treated patients.

Monitor serum glucose levels as clinically appropriate during treatment with TAFINLAR 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.

5.5 Uveitis and Iritis

Uveitis (including iritis) occurred in 1% (6/586) of patients treated with TAFINLAR across clinical trials. 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, and eye pain).

5.6 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.

5.7 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 during treatment and for 4 weeks after treatment 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 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 Cutaneous Malignancies *[see Warnings and Precautions (5.1)]*
- Tumor Promotion in BRAF Wild-Type Melanoma *[see Warnings and Precautions (5.2)]*
- Serious Febrile Drug Reactions *[see Warnings and Precautions (5.3)]*
- Hyperglycemia *[see Warnings and Precautions (5.4)]*
- Uveitis and Iritis *[see Warnings and Precautions (5.5)]*

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 safety of TAFINLAR 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 as monotherapy 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)]*. Trial 1, a multi-center, 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
Gastrointestinal disorders				
Constipation	11	2	14	0
Respiratory, thoracic, and mediastinal disorders				
Cough	12	0	5	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)]

	Dabrafenib N = 187		DTIC N = 59	
	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.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Dabrafenib

Drugs that Inhibit or Induce Drug-Metabolizing Enzymes: Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease, respectively, 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.

Drugs that Affect Gastric pH: 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.

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. Co-administration 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.

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 3 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 (5.7)]*.

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 3 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.

8.5 Geriatric Use

One hundred and twenty-six (22%) of 586 patients in clinical trials of TAFINLAR 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.

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 4 weeks after treatment. 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 (5.7), Drug Interactions (7.1), Use in Specific Populations (8.1)]*.

Infertility:

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

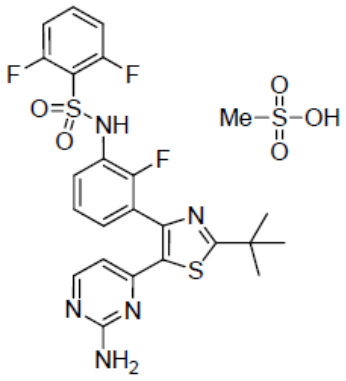
No formal pharmacokinetic trial in patients with renal impairment has been conducted. Dose adjustment is not recommended for patients with mild or moderate renal impairment based on the results of the population pharmacokinetic analysis. An appropriate dose has not been established for patients with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

10 OVERDOSAGE

There is no information on overdosage of TAFINLAR.

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.

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 to 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 have 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 were 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. Co-administration 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%. Co-administration 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. Co-administration 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%. Co-administration 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.

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

In Trial 1, the safety and efficacy of TAFINLAR were demonstrated in an international, multi-center, 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 by mouth 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) vs. 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 duration of follow-up prior to initiation of alternative treatment was 5.1 months and 3.5 months for TAFINLAR and dacarbazine, respectively. 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 5 and Figure 1 summarize the PFS results.

Table 5. Investigator-Assessed Progression-Free Survival and Confirmed Objective Response Results

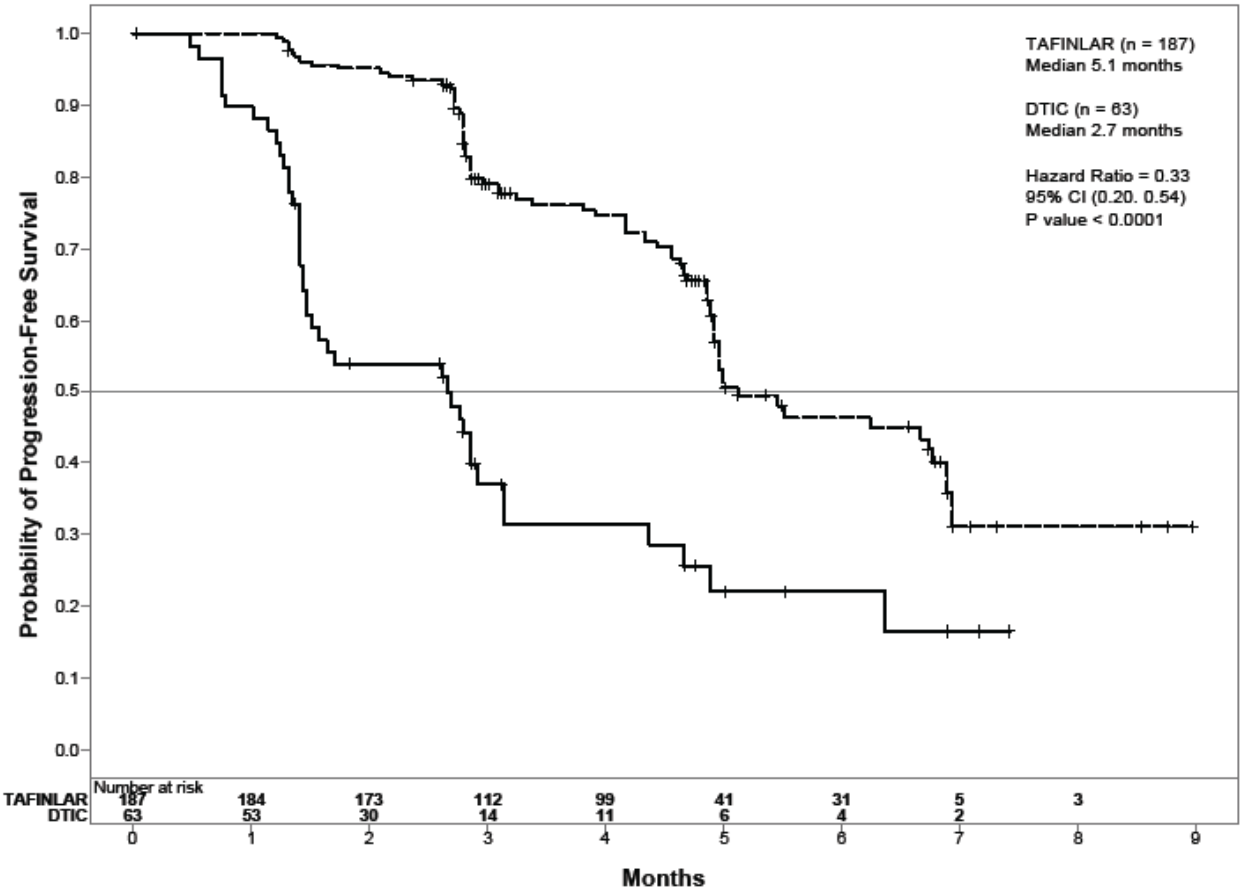
	TAFINLAR N = 187	**Dacarbazine N = 63**
Progression-free Survival		
Objective Response Rate	78 (42%)	41 (65%)
(95% CI)	76	41
CR, n (%)	2	0
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR[a] (95% CI)	0.33 (0.20, 0.54)	
P-value[b]	*P*<0.0001	
Confirmed Tumor Responses		
Number of Events (%)	52%	17%
Progressive Disease	(44, 59)	(9, 29)
Death	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 2). 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 6.

Table 6. Efficacy Results in Patients with BRAF V600E Melanoma Brain Metastases (Trial 2)

	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

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 is indicated *[see Dosage and Administration (2.1)]*.
- TAFINLAR increases the risk of developing new primary cutaneous malignancies. Advise patients to contact their doctor immediately for any new lesions or changes to existing lesions on their skin *[see Warnings and Precautions (5.1)]*.

- TAFINLAR causes pyrexia including serious febrile drug reactions. Instruct patients to contact their doctor if they experience a fever while taking TAFINLAR *[see Warnings and Precautions (5.3)]*.
- 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 (5.4)]*.
- 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 (5.6)]*.
- TAFINLAR can cause fetal harm if taken during pregnancy. Instruct female patients to use non-hormonal, highly effective contraception during treatment and for 4 weeks after treatment. Advise patients to contact their doctor if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see 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)]*.

TAFINLAR is a registered trademark of the GlaxoSmithKline group of companies.

THxID is a trademark of bioMérieux.

GlaxoSmithKline

Research Triangle Park, NC 27709

TFR:XPI

MEDICATION GUIDE

TAFINLAR® (TAFF-in-lar)

(dabrafenib)

capsules

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

TAFINLAR may cause serious side effects, including:

Risk of new cancers. TAFINLAR may cause new cancers, including cutaneous squamous cell carcinoma (cuSCC) that can spread to other parts of the body. Talk with your healthcare provider about your risk for developing skin 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.

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

What is TAFINLAR?

TAFINLAR is a prescription medicine used to treat 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 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 start taking TAFINLAR, tell your healthcare provider if you:

- 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 during treatment and for 4 weeks after stopping TAFINLAR.
    - Birth control using hormones (such as birth control pills, injections, or patches) may not work as well while you are taking TAFINLAR. You should use another effective method of birth control while taking TAFINLAR. Talk to your healthcare provider about birth control methods that may be right for you.
    - Tell your healthcare provider right away if you become pregnant during treatment with TAFINLAR.
- 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.

TAFINLAR may cause lower sperm counts in men. This could affect the ability to father a child. Talk to your healthcare provider if this is a concern for you. Talk to your healthcare provider about family planning options that might be right for you.

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, 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. 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?"**
- **Fever.** TAFINLAR can cause fever, including severe fever. In some cases, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. Tell your healthcare provider right away if you get a fever while taking TAFINLAR.
- **Blood sugar problems.** Some people may develop high blood sugar or worsening diabetes during treatment with TAFINLAR. If you are diabetic, your healthcare provider will check your blood sugar levels before and during treatment with TAFINLAR. Tell your healthcare provider if you have any of the following symptoms of high blood sugar:
    - increased thirst
    - urinating more often than normal
    - your breath smells like fruit

- **Eye problems.** You should have your eyes examined before and while you are taking TAFINLAR. Tell your healthcare provider right away if you get these symptoms during treatment with TAFINLAR:
    - eye pain, swelling, or redness
    - blurred vision or other vision changes during treatment with TAFINLAR

The most common side effects of TAFINLAR include:

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

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 GSK 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).
- Ask your healthcare provider or pharmacist how to safely throw away TAFINLAR that is out of date or no longer needed.

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.

If you would like more information, talk with your healthcare provider. 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 contain: hypromellose, red iron oxide (E172), titanium dioxide (E171).

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

TAFINLAR is a registered trademark of the GlaxoSmithKline group of companies.

GlaxoSmithKline

Research Triangle Park, NC 27709

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