

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)	11/2015
Dosage and Administration (2)	11/2015
Warnings and Precautions (5)	11/2015

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 is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.2, 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. Take TAFINLAR at least 1 hour before or at least 2 hours after a meal. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg, 75 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS and PRECAUTIONS

- New primary malignancies, cutaneous and non-cutaneous:** Can occur when TAFINLAR is administered as a single agent or with trametinib. Monitor patients for new malignancies prior to, or while on therapy, and following discontinuation of treatment. (5.1, 2.3)
- Tumor promotion in BRAF wild-type melanoma:** Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Hemorrhage:** Major hemorrhagic events can occur in patients receiving TAFINLAR with trametinib. Monitor for signs and symptoms of bleeding. (5.3, 2.3)

- Cardiomyopathy:** Assess LVEF before treatment with TAFINLAR and trametinib, after one month of treatment, then every 2 to 3 months thereafter. (5.4, 2.3)
- Uveitis:** Perform ophthalmologic evaluation for any visual disturbances. (5.5, 2.3)
- Serious febrile reactions:** Incidence and severity of pyrexia are increased with TAFINLAR and trametinib. (5.6, 2.3)
- Serious skin toxicity:** Monitor for skin toxicities. Discontinue for intolerable Grade 2, 3, or 4 rash not improving within 3 weeks despite interruption of TAFINLAR. (5.7, 2.3)
- Hyperglycemia:** Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia. (5.8)
- Glucose-6-phosphate dehydrogenase deficiency:** Closely monitor for hemolytic anemia. (5.9)
- Embryo-fetal toxicity:** Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use an effective non-hormonal method of contraception. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

- Most common adverse reactions ($\geq 20\%$) for TAFINLAR as a single agent are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. (6.1)
- Most common adverse reactions ($\geq 20\%$) for TAFINLAR, in combination with trametinib, are pyrexia, rash, chills, headache, arthralgia, and cough. (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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2015

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 **1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma**

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

6 **1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic**
7 **Melanoma**

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

11 **1.3 Limitation of Use**

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

14 **2 DOSAGE AND ADMINISTRATION**

15 **2.1 Patient Selection**

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

21 **2.2 Recommended Dosing**

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

25 Take TAFINLAR at least 1 hour before or 2 hours after a meal [*see Clinical Pharmacology*
26 *(12.3)*]. Do not take a missed dose of TAFINLAR within 6 hours of the next dose of
27 TAFINLAR. Do not open, crush, or break TAFINLAR capsules.

28 **2.3 Dose Modifications**

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

33 For New Primary Cutaneous Malignancies

34 No dose modifications are required.

35 For New Primary Non-Cutaneous Malignancies

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

38 **Table 1. Recommended Dose Reductions**

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

39 **Table 2. Recommended Dose Modifications for TAFINLAR**

Severity of Adverse Reaction ^a	TAFINLAR ^b
<i>Febrile Drug Reaction</i>	
<ul style="list-style-type: none"> • Fever of 101.3°F to 104°F 	Withhold TAFINLAR until fever resolves. Then resume at same or lower dose level.
<ul style="list-style-type: none"> • Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure 	<ul style="list-style-type: none"> • Withhold TAFINLAR until fever resolves. Then resume at a lower dose level. <p>Or</p> <ul style="list-style-type: none"> • Permanently discontinue TAFINLAR.
<i>Cutaneous</i>	
<ul style="list-style-type: none"> • Intolerable Grade 2 skin toxicity • Grade 3 or 4 skin toxicity 	<p>Withhold TAFINLAR for up to 3 weeks.</p> <ul style="list-style-type: none"> • If improved, resume at a lower dose level. • If not improved, permanently discontinue.
<i>Cardiac</i>	
<ul style="list-style-type: none"> • 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.
<i>Uveitis</i>	
<ul style="list-style-type: none"> • Uveitis including iritis and iridocyclitis 	<p>If mild or moderate uveitis does not respond to ocular therapy, or for severe uveitis, withhold TAFINLAR for up to 6 weeks.</p> <ul style="list-style-type: none"> • If improved to Grade 0-1, then resume at the same or at a lower dose level. • If not improved, permanently discontinue.
<i>Other</i>	
<ul style="list-style-type: none"> • Intolerable Grade 2 adverse reactions • Any Grade 3 adverse reaction 	<p>Withhold TAFINLAR.</p> <ul style="list-style-type: none"> • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.

Severity of Adverse Reaction ^a	TAFINLAR ^b
<ul style="list-style-type: none"> First occurrence of any Grade 4 adverse reaction 	<ul style="list-style-type: none"> Withhold TAFINLAR until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. <p style="text-align: center;">Or</p> <ul style="list-style-type: none"> Permanently discontinue TAFINLAR.
<ul style="list-style-type: none"> Recurrent Grade 4 adverse reaction 	Permanently discontinue TAFINLAR.

40 ^a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)
41 version 4.0.

42 ^b See Table 1 for recommended dose reductions of TAFINLAR.

43 **3 DOSAGE FORMS AND STRENGTHS**

44 50 mg capsules: Dark red capsule imprinted with ‘GS TEW’ and ‘50 mg’.

45 75 mg capsules: Dark pink capsule imprinted with ‘GS LHF’ and ‘75 mg’.

46 **4 CONTRAINDICATIONS**

47 None.

48 **5 WARNINGS AND PRECAUTIONS**

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

51 **5.1 New Primary Malignancies**

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

54 Cutaneous Malignancies

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

57 In Trial 1, cutaneous squamous cell carcinomas and keratoacanthomas (cuSCC) occurred in 7%
58 (14/187) of patients receiving TAFINLAR and in none of the patients receiving dacarbazine.

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

64 In Trial 2, the incidence of basal cell carcinoma in patients receiving TAFINLAR in combination
65 with trametinib was 3.3% (7/209) compared with 6% (13/211) of patients receiving single-agent
66 TAFINLAR. The median time to first diagnosis of basal cell carcinoma was 5.1 months (range:
67 2.8 to 23.9 months) in the TAFINLAR plus trametinib arm and was 4.4 months (range: 29 days
68 to 16.5 months) in the single-agent TAFINLAR arm. Among the 7 patients receiving
69 TAFINLAR with trametinib who developed basal cell carcinoma, 2 (29%) experienced more
70 than one occurrence (range: 1 to 3).

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

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

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

82 Non-cutaneous Malignancies

83 Based on its mechanism of action, TAFINLAR may promote the growth and development of
84 malignancies with activation of RAS through mutation or other mechanisms [*see Warnings and*
85 *Precautions (5.2)*]. In Trial 2, non-cutaneous malignancies occurred in 1.4% (3/209) of patients
86 receiving TAFINLAR with trametinib and in 2.8% (6/211) of patients receiving single-agent
87 TAFINLAR.

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

91 **5.2 Tumor Promotion in BRAF Wild-Type Melanoma**

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

97 **5.3 Hemorrhage**

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

100 In Trial 2, the incidence of hemorrhagic events in patients receiving TAFINLAR with trametinib
101 was 19% (40/209) compared with 15% (32/211) of patients receiving single-agent TAFINLAR.
102 Gastrointestinal hemorrhage occurred in 6% (12/209) of patients receiving TAFINLAR with
103 trametinib compared with 3% (6/211) of patients receiving single-agent TAFINLAR. Intracranial
104 hemorrhage was fatal in 1.4% (3/209) of patients receiving TAFINLAR with trametinib
105 compared with none of the patients receiving single-agent TAFINLAR.

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

109 **5.4 Cardiomyopathy**

110 Cardiomyopathy can occur with TAFINLAR.

111 In Trial 2, all patients were required to have an echocardiogram at baseline to document normal
112 left ventricular ejection fraction (LVEF) and serial echocardiograms at Week 4, Week 12, and
113 every 12 weeks thereafter. Cardiomyopathy, defined as a decrease in LVEF $\geq 10\%$ from baseline
114 and below the institutional lower limit of normal, occurred in 6% (12/206) of patients receiving
115 TAFINLAR with trametinib and 2.9% (6/207) of patients receiving single-agent TAFINLAR.
116 The median time to onset of cardiomyopathy on the TAFINLAR plus trametinib arm was 8.2
117 months (range: 28 days to 24.9 months), and was 4.4 months (range: 28 days to 19.1 months) on
118 the TAFINLAR arm.

119 In Trial 2, cardiomyopathy was identified within the first month of initiation of TAFINLAR with
120 trametinib in 2 of 12 patients, and in 2 of 6 patients receiving single-agent TAFINLAR.
121 Development of cardiomyopathy in patients receiving TAFINLAR and trametinib resulted in
122 dose interruption of TAFINLAR (4.4%) or discontinuation of TAFINLAR (1.0%). In patients
123 receiving single-agent TAFINLAR, development of cardiomyopathy resulted in dose
124 interruption (2.4%), dose reduction (0.5%), or discontinuation (1.0%). Cardiomyopathy resolved
125 in 10 of 12 patients receiving TAFINLAR with trametinib, and in 3 of 6 patients receiving
126 single-agent TAFINLAR.

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

134 **5.5 Uveitis**

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

136 Uveitis occurred in 1% (6/586) of patients receiving TAFINLAR across multiple clinical trials
137 and in 2% (9/559) of patients receiving TAFINLAR with trametinib across Trials 2 and 3.
138 Treatment employed in clinical trials included steroid and mydriatic ophthalmic drops.
139 Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia,
140 eye pain). If iritis is diagnosed, administer ocular therapy and continue TAFINLAR without dose
141 modification; for severe uveitis or iridocyclitis, interrupt TAFINLAR and treat as clinically
142 indicated. Permanently discontinue TAFINLAR for persistent Grade 2 or greater uveitis of >6
143 weeks duration [*see Dosage and Administration (2.3)*].

144 **5.6 Serious Febrile Reactions**

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

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

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

155 In Trials 2 and 3, fever occurred in 54% (303/559) of patients receiving TAFINLAR with
156 trametinib; the median time to onset of first occurrence of fever was 1 month (range: 1 day to
157 23.5 months) and the median duration of fever was 3 days (range: 1 day to 11.3 months).
158 Approximately one-half of the patients who received TAFINLAR with trametinib and
159 experienced pyrexia had 3 or more discrete episodes.

160 Serious febrile reactions or fever of any severity complicated by severe rigors/chills,
161 hypotension, dehydration, renal failure, or syncope, occurred in 17% (93/559) of patients
162 receiving TAFINLAR with trametinib. Fever was complicated by severe chills/rigors in 0.4%
163 (2/559), dehydration in 1.8% (10/559), renal failure in 0.5% (3/559), and syncope in 0.7%
164 (4/559) of patients.

165 Withhold TAFINLAR for fever of 101.3°F or higher. Withhold TAFINLAR for any serious
166 febrile reaction or fever complicated by hypotension, rigors or chills, dehydration, or renal
167 failure and evaluate for signs and symptoms of infection. Monitor serum creatinine and other
168 evidence of renal function during and following severe pyrexia. Refer to Table 2 for
169 recommended dose modifications for adverse reactions [*see Dosage and Administration (2.3)*].
170 Administer antipyretics as secondary prophylaxis when resuming TAFINLAR if patient had a
171 prior episode of severe febrile reaction or fever associated with complications. Administer
172 corticosteroids (e.g., prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia

173 if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia
174 associated with complications such as dehydration, hypotension, renal failure or severe
175 chills/rigors, and there is no evidence of active infection.

176 **5.7 Serious Skin Toxicity**

177 Serious skin toxicity can occur with TAFINLAR.

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

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

183 **5.8 Hyperglycemia**

184 Hyperglycemia can occur with TAFINLAR.

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

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

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

197 **5.9 Glucose-6-Phosphate Dehydrogenase Deficiency**

198 TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia
199 in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Monitor patients with
200 G6PD deficiency for signs of hemolytic anemia while taking TAFINLAR.

201 **5.10 Embryo-Fetal Toxicity**

202 Based on findings from animal studies and its mechanism of action, TAFINLAR can cause fetal
203 harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in
204 rats at doses three times greater than the human exposure at the recommended clinical dose. If
205 TAFINLAR is used during pregnancy or if the patient becomes pregnant while taking
206 TAFINLAR, advise the patient of the potential risk to a fetus [*see Use in Specific Populations*
207 (8.1)].

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

213 **6 ADVERSE REACTIONS**

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

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

224 **6.1 Clinical Trials Experience**

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

228 The data described in the Warnings and Precautions section and below reflect exposure to
229 TAFINLAR as a single agent and in combination with trametinib.

230 **TAFINLAR Administered as a Single Agent**

231 The safety of TAFINLAR as a single agent was evaluated in 586 patients with BRAF V600
232 mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who
233 received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable
234 toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for
235 more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-
236 label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg
237 (range: 118 to 300 mg).

238 Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from
239 analyses of Trial 1 [see *Clinical Studies (14.1)*]. Trial 1, a multicenter, international, open-label,
240 randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF

241 V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187)
242 or dacarbazine 1,000 mg/m² intravenously every 3 weeks (n = 63). The trial excluded patients
243 with abnormal left ventricular ejection fraction or cardiac valve morphology (\geq Grade 2),
244 corrected QT interval greater than or equal to 480 milliseconds on electrocardiogram, or a known
245 history of glucose-6-phosphate dehydrogenase deficiency. The median duration on treatment was
246 4.9 months for patients treated with TAFINLAR and 2.8 months for dacarbazine-treated patients.
247 The population exposed to TAFINLAR was 60% male, 99% White, and had a median age of 53
248 years.

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

252 The incidence of adverse events resulting in permanent discontinuation of study medication in
253 Trial 1 was 3% for patients treated with TAFINLAR and 3% for patients treated with
254 dacarbazine. The most frequent (\geq 2%) adverse reactions leading to dose reduction of
255 TAFINLAR were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%).

256 **Table 3. Select Common Adverse Reactions Occurring in $\geq 10\%$ (All Grades) or $\geq 2\%$**
257 **(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

258 ^a Adverse drug reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of
259 toxicity.

260 ^b Grade 4 adverse reactions limited to hyperkeratosis (n = 1) and constipation (n = 1).

261 ^c Includes skin papilloma and papilloma.

262 ^d cuSCC = cutaneous squamous cell carcinoma, includes squamous cell carcinoma of the skin and
263 keratoacanthoma.

264 ^e Cases of cuSCC were required to be reported as Grade 3 per protocol.

265 ^f NA = not applicable.

266

267 **Table 4. Incidence of Laboratory Abnormalities Increased from Baseline Occurring at a**
268 **Higher Incidence in Patients Treated with TAFINLAR in Trial 1 [Between-Arm Difference**
269 **of $\geq 5\%$ (All Grades) or $\geq 2\%$ (Grades 3 or 4)]^a**

Test	TAFINLAR 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 ^b	14	2
Increased alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

270 ^a Adverse drug reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of
271 toxicity.

272 ^b Grade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

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

275 *Gastrointestinal Disorders:* Pancreatitis.

276 *Immune System Disorders:* Hypersensitivity manifesting as bullous rash.

277 *Renal and Urinary Disorders:* Interstitial nephritis.

278 TAFINLAR Administered with Trametinib

279 The safety of TAFINLAR when administered with trametinib was evaluated in 559 patients with
280 previously untreated, unresectable or metastatic, BRAF V600E or V600K mutation-positive
281 melanoma who received TAFINLAR in two trials, Trial 2 (n = 209) a multicenter, double-blind,
282 randomized (1:1), active controlled trial and Trial 3 (n = 350) a multicenter, open-label,
283 randomized (1:1), active controlled trial. In Trials 2 and 3, patients received TAFINLAR 150
284 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or
285 unacceptable toxicity. Both trials excluded patients with abnormal left ventricular ejection
286 fraction, history of acute coronary syndrome within 6 months, history of Class II or greater
287 congestive heart failure (New York Heart Association), history of RVO or RPED, QTcB interval
288 ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases,
289 or a known history of G6PD deficiency [see *Clinical Studies (14.2)*].

290 Among these 559 patients, 199 (36%) were exposed to TAFINLAR for > 6 months to 12 months
291 while 185 (33%) were exposed to TAFINLAR for ≥ 1 year. The median age was 55 years (range:
292 18 to 91), 57% were male, 98% were White, 72% had baseline ECOG performance status 0 and
293 28% had ECOG performance status 1, 64% had M1c stage disease, 35% had elevated LDH at
294 baseline and 0.5% had a history of brain metastases.

295 The most commonly occurring adverse reactions ($\geq 20\%$) for TAFINLAR in patients receiving
296 TAFINLAR plus trametinib in Trials 2 and 3 were: pyrexia, rash, chills, headache, arthralgia,
297 and cough.

298 Table 5 and Table 6 present adverse drug reactions and laboratory abnormalities, respectively,
299 observed in Trial 2.

300 The demographics and baseline tumor characteristics of patients enrolled in Trial 2 are
301 summarized in Clinical Studies [*see Clinical Studies (14.2)*]. Patients receiving TAFINLAR plus
302 trametinib had a median duration of exposure of 11 months (range: 3 days to 30 months) to
303 TAFINLAR. Among the 209 patients receiving TAFINLAR plus trametinib, 26% were exposed
304 to TAFINLAR for >6 months to 12 months while 46% were exposed to TAFINLAR for >1 year.

305 In Trial 2, adverse reactions resulting in discontinuation of TAFINLAR occurred in 11% of
306 patients receiving TAFINLAR plus trametinib; the most common was pyrexia (1.9%). Adverse
307 reactions leading to dose reductions of TAFINLAR occurred in 26% of patients receiving
308 TAFINLAR plus trametinib; the most common were pyrexia (14%), neutropenia (1.9%), rash
309 (1.9%), and chills (1.9%). Adverse reactions leading to dose interruptions of TAFINLAR occurred in
310 56% of patients receiving TAFINLAR plus trametinib; the most common were pyrexia (35%),
311 chills (11%), vomiting (7%), nausea (5%), and decreased ejection fraction (5%).
312

313 **Table 5. Select Adverse Reactions Occurring in ≥10% (All Grades) of Patients Treated**
314 **with TAFINLAR in Combination with Trametinib in Trial 2^a**

Adverse Reactions	Pooled TAFINLAR plus Trametinib N = 559		Trial 2			
	All Grades (%)	Grades 3 and 4 ^b (%)	TAFINLAR plus Trametinib N =209		TAFINLAR N = 211	
			All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General disorders and administrative site conditions						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Gastrointestinal disorders						
Constipation	13	0.2	13	0.5	10	0
Nervous system disorders						
Headache	30	0.9	33	0.5	30	1.4
Dizziness	11	0.2	14	0	7	0
Musculoskeletal, connective tissue, and bone disorders						
Arthralgia	25	0.9	26	0.9	31	0
Myalgia	15	0.2	13	0.5	13	0
Skin and subcutaneous tissue disorders						
Rash ^c	32	1.1	42	0	27	1.4
Dry skin	10	0	12	0	16	0
Respiratory, thoracic, and mediastinal disorders						
Cough	20	0	21	0	21	0
Infections and infestations						
Nasopharyngitis	12	0	12	0	10	0

315 ^a NCI CTCAE version 4

316 ^b Grade 4 adverse reactions limited to headache (n = 1).

317 ^c Includes rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, rash
318 maculo-papular, and rash folliculitis.

319 Other clinically important adverse reactions for TAFINLAR across Trials 2 and 3 (N = 559)
320 observed in less than 10% of patients receiving TAFINLAR in combination with trametinib
321 were:

322 *Gastrointestinal Disorders:* pancreatitis

323 *Subcutaneous Tissue Disorders:* panniculitis

324 **Table 6. Select Treatment-Emergent Laboratory Abnormalities Occurring at ≥10% (All**
325 **Grades) of Patients Receiving TAFINLAR with Trametinib in Trial 2**

Test	Pooled TAFINLAR plus Trametinib N = 559 ^a		Trial 2			
			TAFINLAR plus Trametinib N = 209 ^b		TAFINLAR N = 211 ^b	
	All Grades (%)	Grades 3 and 4 ^c (%)	All Grades (%)	Grades 3 and 4 ^c (%)	All Grades (%)	Grades 3 and 4 ^c (%)
Liver Function Tests						
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypophosphatemia	38	6	38	3.8	35	7
Hyponatremia	25	8	24	6	14	2.9

326 ^a For these laboratory tests the denominator is 556.

327 ^b For these laboratory tests the denominator is 208 for the combination arm, 208-209 for the TAFINLAR arm.

328 ^c Grade 4 adverse reactions limited to hyperglycemia (n = 4), hyponatremia and hypophosphatemia (each n = 1),
329 in the pooled combination arm; hyperglycemia (n = 1) in the Trial 2 combination arm; hypophosphatemia (n = 1)
330 in the TAFINLAR arm.

331 **7 DRUG INTERACTIONS**

332 **7.1 Effects of Other Drugs on Dabrafenib**

333 Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors of CYP3A4 or
334 CYP2C8 may increase concentrations of dabrafenib and strong inducers of CYP3A4 or CYP2C8
335 may decrease concentrations of dabrafenib [see *Clinical Pharmacology (12.3)*]. Substitution of
336 strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is recommended during treatment
337 with TAFINLAR. If concomitant use of strong inhibitors (e.g., ketoconazole, nefazodone,
338 clarithromycin, gemfibrozil) or strong inducers (e.g., rifampin, phenytoin, carbamazepine,
339 phenobarbital, St John's wort) of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely
340 for adverse reactions when taking strong inhibitors or loss of efficacy when taking strong
341 inducers.

342 **7.2 Effects of Dabrafenib on Other Drugs**

343 Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of
344 midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a
345 CYP3A4/CYP1A2 substrate) [see *Clinical Pharmacology (12.3)*]. Monitor international
346 normalized ratio (INR) levels more frequently in patients receiving warfarin during initiation or

347 discontinuation of dabrafenib. Coadministration of TAFINLAR with other substrates of these
348 enzymes, including dexamethasone or hormonal contraceptives, can result in decreased
349 concentrations and loss of efficacy [see *Use in Specific Populations (8.1, 8.3)*]. Substitute for
350 these medications or monitor patients for loss of efficacy if use of these medications is
351 unavoidable.

352 **8 USE IN SPECIFIC POPULATIONS**

353 **8.1 Pregnancy**

354 Risk Summary

355 Based on findings from animal reproduction studies and its mechanism of action, TAFINLAR
356 can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology*
357 *(12.1)*]. There is insufficient data in pregnant women exposed to TAFINLAR to assess the risks.
358 Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human
359 exposure at the recommended clinical dose of 150 mg twice daily [see *Data*]. If TAFINLAR is
360 used during pregnancy or if the patient becomes pregnant while taking TAFINLAR, advise the
361 patient of the potential risk to a fetus.

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

364 Data

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

372 **8.2 Lactation**

373 Risk Summary

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

378 **8.3 Females and Males of Reproductive Potential**

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

381 Contraception

382 *Females*

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

388 Infertility

389 *Females*

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

395 *Males*

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

400 **8.4 Pediatric Use**

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

403 *Juvenile Animal Data*

404 In a repeat-dose toxicity study in juvenile rats, an increased incidence of kidney cysts and tubular
405 deposits were noted at doses as low as 0.2 times the human exposure at the recommended adult
406 dose based on AUC. Additionally, forestomach hyperplasia, decreased bone length, and early
407 vaginal opening were noted at doses as low as 0.8 times the human exposure at the
408 recommended adult dose based on AUC.

409 **8.5 Geriatric Use**

410 One hundred and twenty-six (22%) of 586 patients in clinical trials of TAFINLAR administered
411 as a single agent and 40 (21%) of the 187 patients receiving TAFINLAR in Trial 1 were greater

412 than or equal to 65 years of age. No overall differences in the effectiveness or safety of
413 TAFINLAR were observed in elderly patients as compared to younger patients in Trial 1.

414 Of the 559 patients randomized to receive TAFINLAR plus trametinib in Trials 2 and 3, 24%
415 were aged 65 years and older and 6% patients aged 75 years and older. No overall differences in
416 the effectiveness of TAFINLAR plus trametinib were observed in elderly patients as compared
417 to younger patients. The incidences of peripheral edema (26% vs. 12%) and anorexia (21% vs.
418 9%) were increased in elderly patients as compared to younger patients.

419 **8.6 Hepatic Impairment**

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

426 **8.7 Renal Impairment**

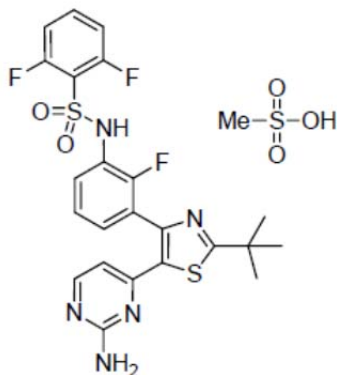
427 No formal pharmacokinetic trial in patients with renal impairment has been conducted. Dose
428 adjustment is not recommended for patients with mild or moderate renal impairment based on
429 the results of the population pharmacokinetic analysis. An appropriate dose has not been
430 established for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

431 **10 OVERDOSAGE**

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

435 **11 DESCRIPTION**

436 Dabrafenib mesylate is a kinase inhibitor. The chemical name for dabrafenib mesylate is N-
437 [5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-
438 difluorobenzene sulfonamide, methanesulfonate salt. It has the molecular formula
439 $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$ and a molecular weight of 615.68. Dabrafenib mesylate has the



440 following chemical structure:

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

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

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

450 **12 CLINICAL PHARMACOLOGY**

451 **12.1 Mechanism of Action**

452 Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC_{50} values of
453 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes,
454 respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC_{50} values of 3.2
455 and 5.0 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher
456 concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E,
457 can result in constitutively activated BRAF kinases that may stimulate tumor cell growth [see
458 *Indications and Usage (1)*]. Dabrafenib inhibits BRAF V600 mutation-positive melanoma cell
459 growth in vitro and in vivo.

460 Dabrafenib and trametinib target two different kinases in the RAS/RAF/MEK/ERK pathway.
461 Use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF

462 V600 mutation-positive melanoma cell lines in vitro and prolonged inhibition of tumor growth in
463 BRAF V600 mutation positive melanoma xenografts compared with either drug alone.

464 **12.2 Pharmacodynamics**

465 Cardiac Electrophysiology

466 A dedicated study to evaluate the QT prolongation potential has not been conducted for
467 TAFINLAR. In clinical trials, QTc (heart rate-corrected QT) prolongation to ≥ 500 ms occurred
468 in 0.8% (2/264) of patients receiving TAFINLAR plus trametinib and in 1.5 % (4/264) of
469 patients receiving TAFINLAR as a single agent. The QTc was increased >60 ms from baseline in
470 3.8% (10/264) of patients receiving TAFINLAR plus trametinib and 3% (8/264) of patients
471 treated with TAFINLAR as a single agent.

472 **12.3 Pharmacokinetics**

473 Absorption

474 After oral administration, median time to achieve peak plasma concentration (T_{max}) is 2 hours.
475 Mean absolute bioavailability of oral dabrafenib is 95%. Following a single dose, dabrafenib
476 exposure (C_{max} and AUC) increased in a dose-proportional manner across the dose range of 12 to
477 300 mg, but the increase was less than dose-proportional after repeat twice-daily dosing. After
478 repeat twice-daily dosing of 150 mg, the mean accumulation ratio was 0.73 and the inter-subject
479 variability (CV%) of AUC at steady-state was 38%.

480 Administration of dabrafenib with a high-fat meal decreased C_{max} by 51%, decreased AUC by
481 31%, and delayed median T_{max} by 3.6 hours as compared with the fasted state [*see Dosage and*
482 *Administration (2.2)*].

483 Distribution

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

486 Metabolism

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

496 Elimination

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

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

504 Specific Populations

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

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

509 *Renal Impairment:* No formal pharmacokinetic trial in patients with renal impairment has been
510 conducted. The pharmacokinetics of dabrafenib were evaluated using a population analysis in
511 233 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 m²) and 30 patients with
512 moderate renal impairment (GFR 30 to 59 mL/min/1.73 m²) enrolled in clinical trials. Mild or
513 moderate renal impairment has no effect on systemic exposure to dabrafenib and its metabolites.
514 No data are available in patients with severe renal impairment.

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

520 Drug Interactions

521 *Effect of Strong Inhibitors of CYP3A4 or CYP2C8 on Dabrafenib:* In vitro studies show that
522 dabrafenib is a substrate of CYP3A4 and CYP2C8 while hydroxy-dabrafenib and desmethyl-
523 dabrafenib are CYP3A4 substrates. Coadministration of dabrafenib 75 mg twice daily and
524 ketoconazole 400 mg once daily (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib
525 AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%.
526 Coadministration of dabrafenib 75 mg twice daily and gemfibrozil 600 mg twice daily (a strong
527 CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of
528 dabrafenib metabolites.

529 *Effect of Dabrafenib on CYP Substrates:* In vitro data demonstrate that dabrafenib is an inducer
530 of CYP3A4 and CYP2B6 via activation of the pregnane X receptor (PXR) and constitutive
531 androstane receptor (CAR) nuclear receptors. Dabrafenib may also induce CYP2C enzymes via

532 the same mechanism. Coadministration of dabrafenib 150 mg twice daily for 15 days and a
533 single dose of midazolam 3 mg (a CYP3A4 substrate) decreased midazolam AUC by 74%.
534 Coadministration of dabrafenib 150 mg twice daily for 15 days and a single dose of warfarin 15
535 mg decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin
536 (a CYP3A4/CYP1A2 substrate) by 33% [see *Drug Interactions (7.2)*].

537 *Effect of Transporters on Dabrafenib:* Dabrafenib is a substrate of human P-glycoprotein (P-gp)
538 and breast cancer resistance protein (BCRP), but is not a substrate of organic cation transporter
539 (OCT1) or organic anion transporting polypeptide (OATP1B1, OATP1B3, OATP2B1) in vitro.
540 Hydroxy-dabrafenib and desmethyl-dabrafenib are not substrates of OATP1B1 or OATP1B3 in
541 vitro.

542 *Effect of Dabrafenib on Transporters:* Dabrafenib and its metabolites, hydroxy-dabrafenib,
543 carboxy-dabrafenib, and desmethyl-dabrafenib, are inhibitors of OATP1B1, OATP1B3 and
544 organic anion transporter (OAT1 and OAT3) in vitro. Dabrafenib and desmethyl-dabrafenib are
545 inhibitors of BCRP in vitro.

546 *Effect of Trametinib on Dabrafenib:* Coadministration of trametinib 2 mg daily with dabrafenib
547 150 mg twice daily resulted in a 23% increase in AUC of dabrafenib, a 33% increase in AUC of
548 desmethyl-dabrafenib, and no change in AUC of hydroxy-dabrafenib as compared with
549 administration of dabrafenib.

550 *Effect of Acid Reducing Agents on Dabrafenib:* Drugs that alter the pH of the upper GI tract (e.g.,
551 proton pump inhibitors, H₂-receptor antagonists, antacids) may alter the solubility of dabrafenib
552 and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate
553 the effect of gastric pH-altering agents on the systemic exposure of dabrafenib. When
554 TAFINLAR is coadministered with a proton pump inhibitor, H₂-receptor antagonist, or antacid,
555 systemic exposure of dabrafenib may be decreased and the effect on efficacy of TAFINLAR is
556 unknown.

557 **13 NONCLINICAL TOXICOLOGY**

558 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

567 noted in pregnant females at 300 mg/kg/day (which is approximately three times the human
568 exposure at the recommended dose based on AUC).

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

572 **13.2 Animal Toxicology and/or Pharmacology**

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

578 **14 CLINICAL STUDIES**

579 **14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma –** 580 **TAFINLAR Administered as a Single Agent**

581 In Trial 1, the safety and efficacy of TAFINLAR as a single agent were demonstrated in an
582 international, multicenter, randomized (3:1), open-label, active-controlled trial conducted in 250
583 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic
584 melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded.
585 Patients were randomized to receive TAFINLAR 150 mg orally twice daily (n = 187) or
586 dacarbazine 1,000 mg/m² intravenously every 3 weeks (n = 63). Randomization was stratified by
587 disease stage at baseline [unresectable Stage III (regional nodal or in-transit metastases), M1a
588 (distant skin, subcutaneous, or nodal metastases), or M1b (lung metastases) versus M1c
589 melanoma (all other visceral metastases or elevated serum LDH)]. The main efficacy outcome
590 measure was progression-free survival (PFS) as assessed by the investigator. In addition, an
591 independent radiology review committee (IRRC) assessed the following efficacy outcome
592 measures in pre-specified supportive analyses: PFS, confirmed objective response rate (ORR),
593 and duration of response.

594 The median age of patients in Trial 1 was 52 years. The majority of the trial population was male
595 (60%), White (99%), had an ECOG performance status of 0 (67%), M1c disease (66%), and
596 normal LDH (62%). All patients had tumor tissue with mutations in BRAF V600E as determined
597 by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were
598 tested retrospectively, using an FDA-approved companion diagnostic test, THxID™-BRAF
599 assay.

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

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

606

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

Investigator-Assessed Endpoints [†]	TAFINLAR N = 187	Dacarbazine N = 63
Progression-Free Survival		
Number of Events (%)	78 (42%)	41 (65%)
Progressive Disease	76	41
Death	2	0
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR ^a (95% CI)	0.33 (0.20, 0.54)	
<i>P</i> -value ^b	<i>P</i> <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)

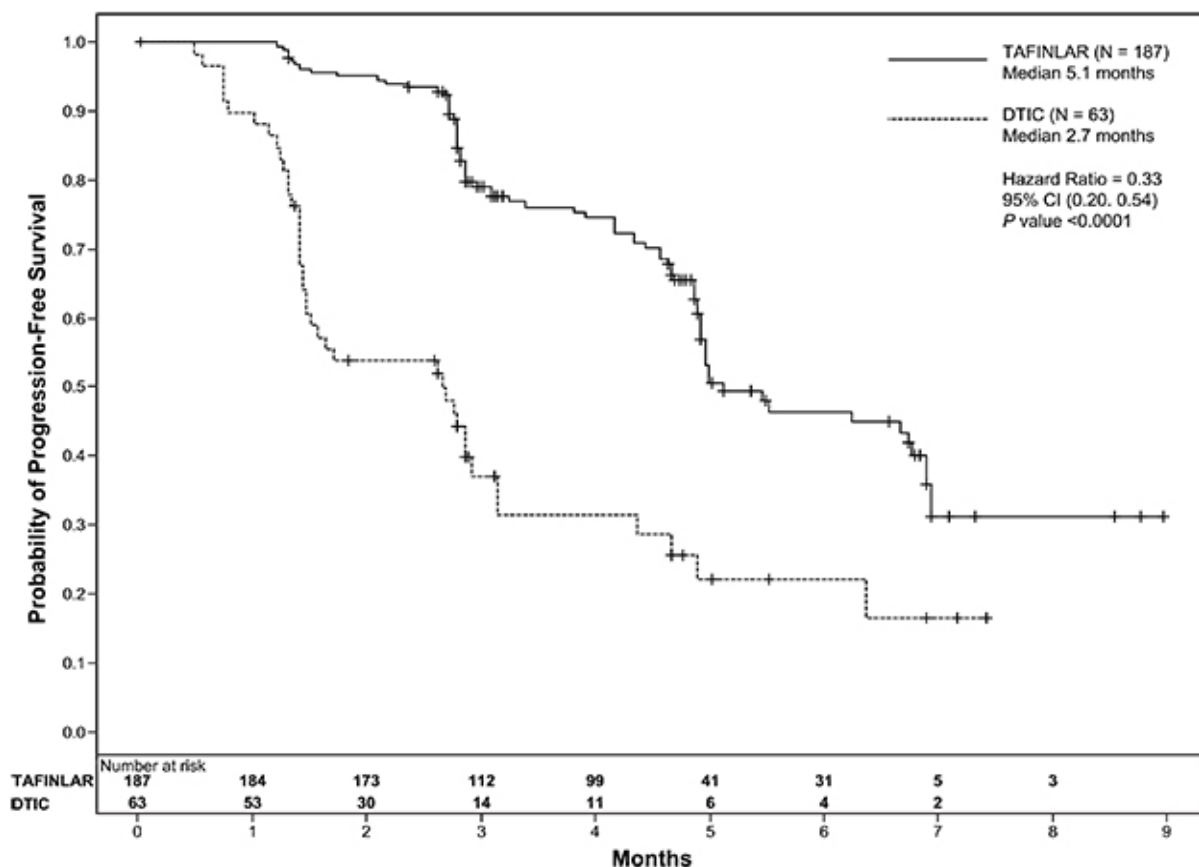
609 [†] CI = Confidence interval; HR = Hazard ratio; CR = Complete response; PR = Partial
610 response; NR = Not reached.

611 ^a Pike estimator, stratified by disease state.

612 ^b Stratified log-rank test.

613

614 **Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival in**
615 **Trial 1**



616

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

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

632 The median age of patients in Cohort A was 50 years, 72% were male, 100% were White, 59%
633 had a pre-treatment ECOG performance status of 0, and 57% had an elevated LDH value at
634 baseline. The median age of patients in Cohort B was 51 years, 63% were male, 98% were
635 White, 66% had a pre-treatment ECOG performance status of 0, and 54% had an elevated LDH
636 value at baseline. Efficacy results as determined by an independent radiology review committee,
637 masked to investigator response assessments, are provided in Table 8.

638
639

Table 8. Efficacy Results in Patients with BRAF V600E Melanoma Brain Metastases

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

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

641 **14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma – TAFINLAR**
642 **Administered with Trametinib**

643 The safety and efficacy of TAFINLAR administered with trametinib were evaluated in two
644 international, randomized, active-controlled trials: one double-blind trial (Trial 2) and one open-
645 label trial (Trial 3).

646 Trial 2 compared TAFINLAR and trametinib to TAFINLAR and placebo as first-line therapy for
647 patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K
648 mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR
649 150 mg twice daily and trametinib 2 mg once daily or TAFINLAR 150 mg twice daily plus
650 matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (> the
651 upper limit of normal (ULN) vs. ≤ULN) and BRAF mutation subtype (V600E vs. V600K). The
652 major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST
653 v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall
654 response rate (ORR).

655 Trial 3 compared TAFINLAR and trametinib to vemurafenib as first-line treatment therapy for
656 patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K
657 mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive TAFINLAR
658 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily.
659 Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal
660 (ULN) vs. ≤ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy
661 outcome measure was overall survival. Additional efficacy outcome measures were PFS and
662 ORR as assessed by investigator per RECIST v1.1.

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

669 In Trial 3, 704 patients were randomized to TAFINLAR plus trametinib (n = 352) or single-agent
670 vemurafenib (n = 352). The median age was 55 years (range: 18 to 91 years), 96% were White,
671 and 55% were male, 6% percent of patients had Stage IIIC, 61% had M1c disease, 67% had a
672 normal LDH, 70% had ECOG performance status of 0, 89% had BRAF V600E mutation-
673 positive melanoma, and one patient had a history of brain metastases.

674 Trial 2 and Trial 3 demonstrated statistically significant improvements in OS and PFS (see Table
675 9 and Figures 2 and 3).

676 **Table 9. Efficacy Results in Patients with BRAF V600E or V600K Melanoma^a**

Endpoint [†]	Trial 2		Trial 3	
	TAFINLAR plus Trametinib N=211	TAFINLAR plus Placebo N=212	TAFINLAR plus Trametinib N=352	Vemurafenib N=352
Overall Survival				
Number of deaths (%)	99 (47%)	123 (58%)	100 (28%)	122 (35%)
Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.1)	NR (18.3, NR)	17.2 (16.4, NR)
HR (95% CI)	0.71 (0.55, 0.92)		0.69 (0.53, 0.89)	
<i>P</i> value (log-rank test)	0.01		0.005 ^a	
Progression-Free Survival (PFS)^b				
Number of events (%)	102 (48%)	109 (51%)	166 (47%)	217 (62%)
Median, months (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
HR (95% CI)	0.75 (0.57, 0.99)		0.56 (0.46, 0.69)	
<i>P</i> value (log-rank test)	0.035		<0.001	
Overall Response Rate (ORR)^b				
ORR, % (95% CI)	66 (60, 73)	51 (44, 58)	64 (59, 69)	51 (46, 56)
<i>P</i> value	<0.001		<0.001	
CR, %	10	8	13	8
PR, %	56	42	51	43
Median duration of response, months (95% CI)	9.2 (7.4, NR)	10.2 (7.5, NR)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

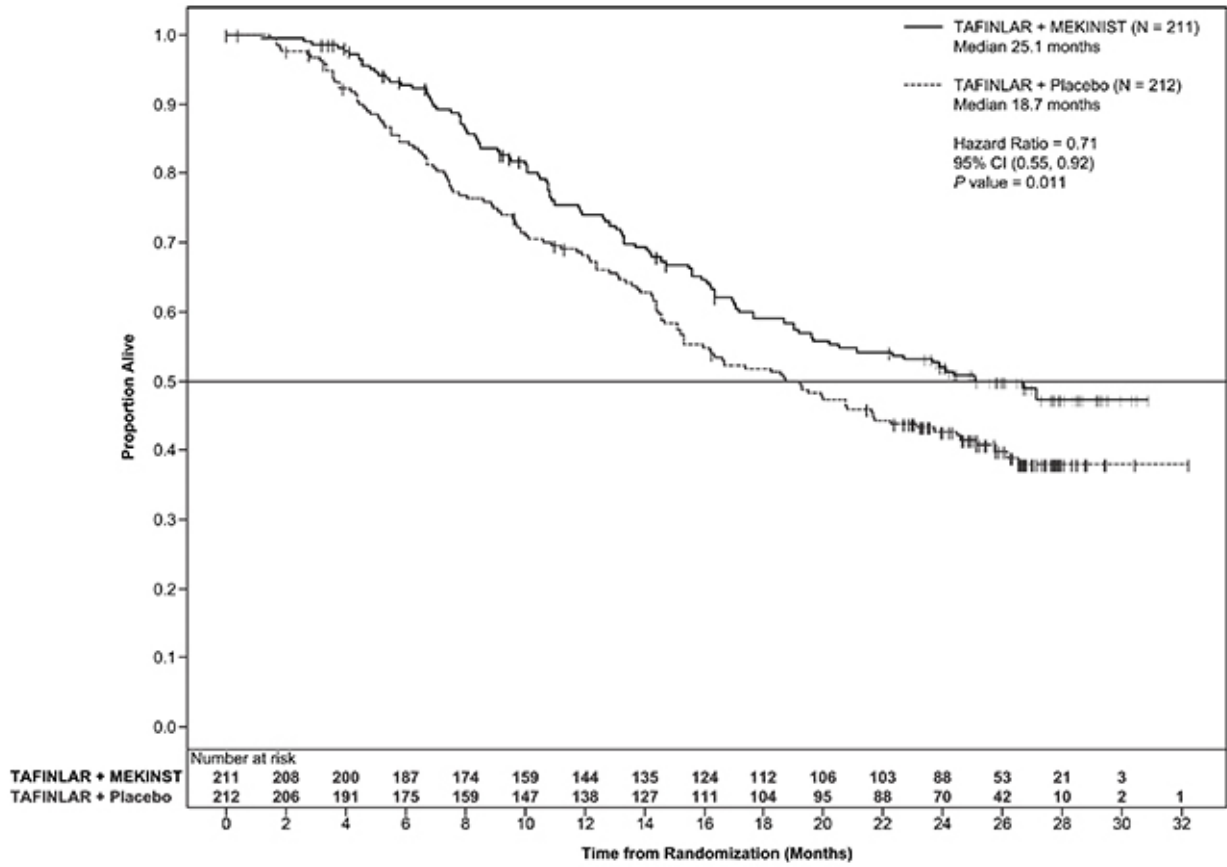
677 [†] CI = Confidence interval; HR = Hazard ratio; CR = Complete response; PR = Partial
678 response; NR = Not reached.

679 ^a *P*-value is comparing with the allocated alpha of 0.021 for the interim analysis based on 77%
680 information.

681 ^b PFS and ORR were assessed by investigator.

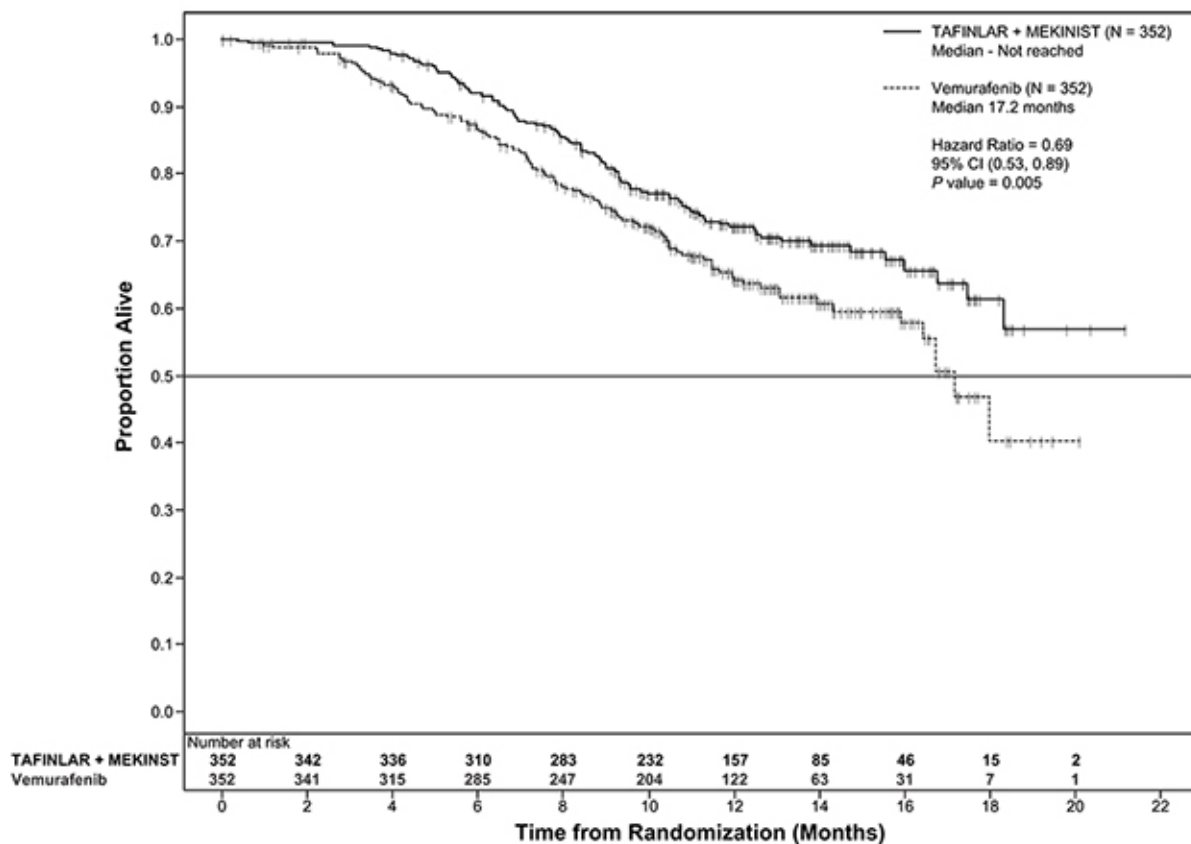
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683 **Figure 2. Kaplan-Meier Curves for Overall Survival in Trial 2**



684

685 **Figure 3. Kaplan-Meier Curves for Overall Survival in Trial 3**



686

687 **16 HOW SUPPLIED/STORAGE AND HANDLING**

688 50 mg capsules: Dark red capsule imprinted with 'GS TEW' and '50 mg' available in bottles of
689 120 (NDC 0173-0846-08). Each bottle contains a silica gel desiccant.

690 75 mg capsules: Dark pink capsule imprinted with 'GS LHF' and '75 mg' available in bottles of
691 120 (NDC 0173-0847-08). Each bottle contains a silica gel desiccant.

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

694 **17 PATIENT COUNSELING INFORMATION**

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

696 Inform patients of the following:

697 Confirmation of BRAF V600E or V600K mutation

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

- 701 • TAFINLAR with trametinib: Evidence of BRAF V600 mutation in tumor specimens
702 using an FDA-approved test is necessary to identify patients for whom treatment is
703 indicated [*see Dosage and Administration (2.1)*].

704 New cutaneous and non-cutaneous malignancies

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

709 Hemorrhage

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

714 Cardiomyopathy

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

717 Uveitis

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

721 Serious febrile reactions

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

726 Serious skin toxicities

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

729 Hyperglycemia

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

733 Glucose-6-phosphate dehydrogenase (G6PD) deficiency

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

737 Embryo-fetal toxicity

738 TAFINLAR can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the
739 potential risk to a fetus [see *Warnings and Precautions (5.10)*, *Use in Specific Populations (8.1*,
740 *8.3)*].

741 Females and males of reproductive potential

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

747 Infertility

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

750 Lactation

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

753 Instructions for taking Tafinlar

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

756 TAFINLAR is a registered trademark of the GSK group of companies.

757 THxID™ is a trademark of bioMérieux.



758

759 GlaxoSmithKline

760 Research Triangle Park, NC 27709

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

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

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

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

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

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

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

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

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

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

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

See "[What are the possible side effects of TAFINLAR?](#)" for more information about side effects.

What is TAFINLAR?

TAFINLAR is a prescription medicine used alone or with a medicine called trametinib, to treat people with a type of skin cancer called melanoma:

- that has spread to other parts of the body or cannot be removed by surgery, and
- that has a certain type of abnormal "BRAF" gene.

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

TAFINLAR alone or 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 alone or TAFINLAR with trametinib is safe and effective in children.

What should I tell my healthcare provider before taking TAFINLAR?

Before you take TAFINLAR, tell your healthcare provider if you:

- have had bleeding problems
- have heart problems
- have eye problems
- have liver or kidney problems
- have diabetes
- plan to have surgery, dental, or other medical procedures

- have a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme
- have any other medical conditions are pregnant or plan to become pregnant. TAFINLAR can harm your unborn baby.
 - Females who are able to become pregnant should use birth control (contraception) during treatment with TAFINLAR, and for 2 weeks after the last dose of TAFINLAR alone, **or** for 4 months after the last dose when taking TAFINLAR with trametinib.
 - Birth control methods that contain hormones (such as birth control pills, injections, or patches) may not work as well during treatment with TAFINLAR alone or TAFINLAR and trametinib. You should use another effective method of birth control during treatment with TAFINLAR alone or TAFINLAR and trametinib.
 - Talk to your healthcare provider about birth control methods that may be right for you during this time.
 - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with TAFINLAR alone or TAFINLAR and trametinib.
- are breastfeeding or plan to breastfeed. It is not known if TAFINLAR passes into your breast milk.
 - Do not breastfeed during treatment and for 2 weeks after your last dose of TAFINLAR alone, **or** for 4 months after your last dose of TAFINLAR with trametinib. Talk to your healthcare provider about the best way to feed your baby during this time.

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

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

How should I take TAFINLAR?

- Take TAFINLAR exactly as your healthcare provider tells you. Do not change your dose or stop TAFINLAR unless your healthcare provider tells you.
- Take TAFINLAR 2 times a day, about 12 hours apart.
- Take TAFINLAR at least 1 hour before or 2 hours after a meal.
- Do not open, crush, or break TAFINLAR capsules.
- If you miss a dose of TAFINLAR, take it as soon as you remember. 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.

What are the possible side effects of TAFINLAR?

TAFINLAR may cause serious side effects, including:

- **See “What is the most important information I should know about TAFINLAR?”**
- TAFINLAR, when taken with trametinib, can cause serious bleeding problems, especially in your brain or stomach, and can lead to death. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
 - headaches, dizziness, or feeling weak

- cough up blood or blood clots
- vomit blood or your vomit looks like “coffee grounds”
- red or black stool that looks like tar
- **heart problems**, including heart failure. Your healthcare provider should check your heart function before and during treatment with TAFINLAR. Call your healthcare provider right away if you have any of the following signs and symptoms of a heart problem:
 - feeling like your heart is pounding or racing
 - shortness of breath
 - swelling of your ankles or feet
 - feeling lightheaded
- **eye problems**. TAFINLAR, when taken alone or with trametinib, can cause severe eye problems that can lead to blindness. Call your healthcare provider right away if you get these symptoms of eye problems:
 - blurred vision, loss of vision, or other vision changes
 - see color dots
 - halo (see blurred outline around objects)
 - eye pain, swelling, or redness
- **fever**. Fever is common during treatment with TAFINLAR alone or with trametinib, but may also be serious. When taking TAFINLAR with trametinib, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. Call your healthcare provider right away if you get a fever during treatment with TAFINLAR.
- **skin reactions**. Rash is a common side effect of TAFINLAR when taken alone, or with trametinib. TAFINLAR, when taken alone or with trametinib, can also cause other skin reactions. In some cases these rashes and other skin reactions can be severe, and may need to be treated in a hospital. Call your healthcare provider if you get any of the following symptoms:
 - skin rash that bothers you or does not go away
 - acne
 - redness, swelling, peeling, or tenderness of hands or feet
 - skin redness
- **increased blood sugar (hyperglycemia)**. Some people may develop high blood sugar or worsening diabetes during treatment with TAFINLAR, alone or with trametinib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with TAFINLAR alone or with trametinib. Your diabetes medicine may need to be changed. Tell your healthcare provider if you have any of the following symptoms of severe high blood sugar:
 - increased thirst
 - urinating more often than normal, or urinating an increased amount of urine
- TAFINLAR may cause healthy red blood cells to break down too early in people with G6PD deficiency. This may lead to a type of anemia called hemolytic anemia where the body does not have enough healthy red blood cells. Tell your healthcare provider if you have any of the following signs or symptoms:
 - yellow skin (jaundice)

- weakness or dizziness
- shortness of breath

The most common side effects of TAFINLAR alone or with trametinib include:

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

TAFINLAR may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

TAFINLAR may cause lower sperm counts in males. This could affect the ability to father a child. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of TAFINLAR. For more information about side effects, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TAFINLAR?

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

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

General information about the safe and effective use of TAFINLAR

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

What are the ingredients in TAFINLAR?

Active ingredient: dabrafenib

Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose

Capsule shells: hypromellose, red iron oxide (E172), titanium dioxide (E171).



GlaxoSmithKline

Research Triangle Park, NC 27709

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