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RESEARCH**

APPLICATION NUMBER:

202806Orig1s000

LABELING

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 ($\geq 20\%$) 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: 05/2013

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

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

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

7 **2 DOSAGE AND ADMINISTRATION**

8 **2.1 Patient Selection**

9 Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of
10 treatment with TAFINLAR [*see Warnings and Precautions (5.2)*]. Information on FDA-
11 approved tests for the detection of BRAF V600 mutations in melanoma is available at
12 <http://www.fda.gov/CompanionDiagnostics>.

13 **2.2 Recommended Dosing**

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

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

19 **2.3 Dose Modifications**

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

21

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

Target Organ	Adverse Reactions ^a	Dose Modification
Febrile Drug Reaction	<ul style="list-style-type: none"> Fever of 101.3°F to 104°F 	Withhold TAFINLAR until adverse reaction resolves. Then resume TAFINLAR at same dose or at a reduced dose level (see Table 2).
	<ul style="list-style-type: none"> Fever higher than 104°F Fever complicated by rigors, hypotension, dehydration, or renal failure 	Either <ul style="list-style-type: none"> Permanently discontinue TAFINLAR Or <ul style="list-style-type: none"> Withhold TAFINLAR until adverse reaction resolves. Then resume TAFINLAR at a reduced dose level (see Table 2).
Other	<ul style="list-style-type: none"> Intolerable Grade 2 Adverse Reactions Any Grade 3 Adverse Reactions 	<ul style="list-style-type: none"> Withhold TAFINLAR until adverse reaction resolves to Grade 1 or less. Then resume TAFINLAR at a reduced dose level (see Table 2).
	<ul style="list-style-type: none"> First occurrence of Any Grade 4 Adverse Reaction 	Either <ul style="list-style-type: none"> Permanently discontinue TAFINLAR Or <ul style="list-style-type: none"> Withhold TAFINLAR until adverse reaction resolves to Grade 1 or less. Then resume TAFINLAR at a reduced dose level (see Table 2).
	<ul style="list-style-type: none"> 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

24 ^a Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

25

26 **Table 2: Recommended TAFLINAR Dose Reductions**

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

27

28 **3 DOSAGE FORMS AND STRENGTHS**

29 50 mg Capsules: Dark red capsule imprinted with ‘GS TEW’ and ‘50 mg’.

30 75 mg Capsules: Dark pink capsule imprinted with ‘GS LHF’ and ‘75 mg’.

31 **4 CONTRAINDICATIONS**

32 None.

33 **5 WARNINGS AND PRECAUTIONS**

34 **5.1 New Primary Cutaneous Malignancies**

35 TAFINLAR results in an increased incidence of cutaneous squamous cell carcinoma,
36 keratoacanthoma, and melanoma. In Trial 1, cutaneous squamous cell carcinomas and
37 keratoacanthomas (cuSCC) occurred in 7% (14/187) of patients treated with TAFINLAR and in
38 none of the patients treated with dacarbazine. Across clinical trials of TAFINLAR (n = 586), the
39 incidence of cuSCC was 11%. The median time to first cuSCC was 9 weeks (range: 1 to 53
40 weeks). Of those patients who developed a cuSCC, approximately 33% developed one or more
41 cuSCC with continued TAFINLAR. The median time between diagnosis of the first cuSCC and
42 the second cuSCC was 6 weeks.

43 In Trial 1, the incidence of new primary malignant melanomas was 2% (3/187) for patients
44 receiving TAFINLAR while no chemotherapy-treated patient was diagnosed with new primary
45 malignant melanoma.

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

48 **5.2 Tumor Promotion in BRAF Wild-Type Melanoma**

49 In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and
50 increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors.
51 Confirm evidence of BRAF V600E mutation status prior to initiation of TAFINLAR [see
52 *Indications and Usage (1) and Dosage and Administration (2.1)*].

53 **5.3 Serious Febrile Drug Reactions**

54 In Trial 1, serious febrile drug reactions, defined as serious cases of fever or fever of any severity
55 accompanied by hypotension, rigors or chills, dehydration, or renal failure in the absence of
56 another identifiable cause (e.g., infection) occurred in 3.7% (7/187) of patients treated with
57 TAFINLAR and in none of the patients treated with dacarbazine. The incidence of fever (serious
58 and non-serious) was 28% in patients treated with TAFINLAR and 10% in patients treated with
59 dacarbazine. In patients treated with TAFINLAR, the median time to initial onset of fever (any
60 severity) was 11 days (range: 1 to 202 days) and the median duration of fever was 3 days (range
61 1 to 129 days).

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

66 **5.4 Hyperglycemia**

67 Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycemic
68 agent therapy can occur with TAFINLAR. In Trial 1, five of 12 patients with a history of
69 diabetes required more intensive hypoglycemic therapy while taking TAFINLAR. The incidence
70 of Grade 3 hyperglycemia based on laboratory values was 6% (12/187) in patients treated with
71 TAFINLAR compared to none of the dacarbazine-treated patients.

72 Monitor serum glucose levels as clinically appropriate during treatment with TAFINLAR in
73 patients with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of
74 severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of
75 urination.

76 **5.5 Uveitis and Iritis**

77 Uveitis (including iritis) occurred in 1% (6/586) of patients treated with TAFINLAR across
78 clinical trials. Symptomatic treatment employed in clinical trials included steroid and mydriatic
79 ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (e.g., change in
80 vision, photophobia, and eye pain).

81 **5.6 Glucose-6-Phosphate Dehydrogenase Deficiency**

82 TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia
83 in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Closely observe
84 patients with G6PD deficiency for signs of hemolytic anemia.

85 **5.7 Embryofetal Toxicity**

86 Based on its mechanism of action, TAFINLAR can cause fetal harm when administered to a
87 pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times
88 greater than the human exposure at the recommended clinical dose. If this drug is used during

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

91 Advise female patients of reproductive potential to use a highly effective non-hormonal method
92 of contraception during treatment and for 4 weeks after treatment since TAFINLAR can render
93 hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they
94 become pregnant, or if pregnancy is suspected, while taking TAFINLAR [see *Drug Interactions*
95 (7.2), *Use in Specific Populations* (8.6)].

96 **6 ADVERSE REACTIONS**

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

- 98 • New Primary Cutaneous Malignancies [see *Warnings and Precautions* (5.1)]
- 99 • Tumor Promotion in BRAF Wild-Type Melanoma [see *Warnings and Precautions* (5.2)]
- 100 • Serious Febrile Drug Reactions [see *Warnings and Precautions* (5.3)]
- 101 • Hyperglycemia [see *Warnings and Precautions* (5.4)]
- 102 • Uveitis and Iritis [see *Warnings and Precautions* (5.5)]

103

104 **6.1 Clinical Trials Experience**

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

108 The safety of TAFINLAR was evaluated in 586 patients with BRAF V600 mutation-positive
109 unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR
110 150 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity,
111 including 181 patients treated for at least 6 months and 86 additional patients treated for more
112 than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label,
113 randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range:
114 118 to 300 mg).

115 Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from
116 analyses of Trial 1 [see *Clinical Studies* (14)]. Trial 1, a multi-center, international, open-label,
117 randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF
118 V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187)
119 or dacarbazine 1,000 mg/m² intravenously every 3 weeks (n = 63). The trial excluded patients
120 with abnormal left ventricular ejection fraction or cardiac valve morphology (≥Grade 2),
121 corrected QT interval ≥480 milliseconds on electrocardiogram, or a known history of glucose-6-
122 phosphate dehydrogenase deficiency. The median duration on treatment was 4.9 months for

123 patients treated with TAFINLAR and 2.8 months for dacarbazine-treated patients. The
124 population exposed to TAFINLAR was 60% male, 99% white, and had a median age of 53
125 years.

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

129 The incidence of adverse events resulting in permanent discontinuation of study medication in
130 Trial 1 was 3% for patients treated with TAFINLAR and 3% for patients treated with
131 dacarbazine. The most frequent ($\geq 2\%$) adverse reactions leading to dose reduction of
132 TAFINLAR were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%).
133

134 **Table 3. Selected Common Adverse Reactions Occurring in ≥10% (All Grades) or ≥2%**
 135 **(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

136 ^a Adverse drug reactions, reported using MedDRA and graded using CTCAE version 4.0 for
 137 assessment of toxicity.

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

139 ^c Includes skin papilloma and papilloma.

140 ^d Includes squamous cell carcinoma of the skin and keratoacanthoma.

141 ^e Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per
 142 protocol.

143 ^f NA=not applicable

144
145
146
147

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 $\geq 5\%$ (All Grades) or $\geq 2\%$ (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

148
149

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

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

152 *Gastrointestinal Disorders:* Pancreatitis.

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

154 *Renal and Urinary Disorders:* Interstitial nephritis.

155 **7 DRUG INTERACTIONS**

156 **7.1 Effects of Other Drugs on Dabrafenib**

157 Drugs that Inhibit or Induce Drug-Metabolizing Enzymes: Dabrafenib is primarily
158 metabolized by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8
159 may increase or decrease, respectively, concentrations of dabrafenib [*see Clinical Pharmacology*
160 (12.3)]. Substitution of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is
161 recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors (e.g.,
162 ketoconazole, nefazodone, clarithromycin, gemfibrozil) or strong inducers (e.g., rifampin,
163 phenytoin, carbamazepine, phenobarbital, St John’s wort) of CYP3A4 or CYP2C8 is
164 unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors or loss
165 of efficacy when taking strong inducers.

166 Drugs that Affect Gastric pH: Drugs that alter the pH of the upper GI tract (e.g., proton pump
167 inhibitors, H₂-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its
168 bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of
169 gastric pH-altering agents on the systemic exposure of dabrafenib. When TAFINLAR is

170 coadministered with a proton pump inhibitor, H₂-receptor antagonist, or antacid, systemic
171 exposure of dabrafenib may be decreased and the effect on efficacy of TAFINLAR is unknown.

172 **7.2 Effects of Dabrafenib on Other Drugs**

173 Dabrafenib induces CYP3A4 and may induce other enzymes including CYP2B6, CYP2C8,
174 CYP2C9, CYP2C19, and UDP glucuronosyltransferases (UGT) and may induce transporters.
175 Dabrafenib decreased the maximum concentration (C_{max}) and area under the curve (AUC) of
176 midazolam (a substrate of CYP3A4) by 61% and 74%, respectively [*see Clinical Pharmacology*
177 *(12.3)*]. Coadministration of TAFINLAR with other substrates of these enzymes, including
178 warfarin, dexamethasone, or hormonal contraceptives, can result in decreased concentrations and
179 loss of efficacy [*see Use in Specific Populations (8.1, 8.6)*]. Substitute for these medications or
180 monitor patients for loss of efficacy if use of these medications is unavoidable.

181 **8 USE IN SPECIFIC POPULATIONS**

182 **8.1 Pregnancy**

183 Pregnancy Category D

184 **Risk Summary:** Based on its mechanism of action, TAFINLAR can cause fetal harm when
185 administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses
186 3 times greater than the human exposure at the recommended clinical dose of 150 mg twice daily
187 based on AUC. If this drug is used during pregnancy or if the patient becomes pregnant while
188 taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Warnings*
189 *and Precautions (5.7)*].

190 **Animal Data:** In a combined female fertility and embryofetal development study in rats,
191 developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in
192 thymic shape at a dabrafenib dose of 300 mg/kg/day (approximately 3 times the human exposure
193 at the recommended dose based on AUC). At doses of 20 mg/kg/day or greater, (equivalent to
194 the human exposure at the recommended dose based on AUC) rats demonstrated delays in
195 skeletal development and reduced fetal body weight.

196 **8.3 Nursing Mothers**

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

201 **8.4 Pediatric Use**

202 The safety and effectiveness of TAFINLAR have not been established in pediatric patients.

203 **8.5 Geriatric Use**

204 One hundred and twenty-six (22%) of 586 patients in clinical trials of TAFINLAR and 40 (21%)
205 of the 187 patients receiving TAFINLAR in Trial 1 were ≥ 65 years of age. No overall
206 differences in the effectiveness or safety of TAFINLAR were observed in the elderly in Trial 1.

207 **8.6 Females and Males of Reproductive Potential**

208 Contraception:

209 Females

210 Advise female patients of reproductive potential to use highly effective contraception during
211 treatment and for 4 weeks after treatment. Counsel patients to use a non-hormonal method of
212 contraception since TAFINLAR can render hormonal contraceptives ineffective. Advise patients
213 to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while
214 taking TAFINLAR [see *Warnings and Precautions (5.7)*, *Drug Interactions (7.1)*, *Use in*
215 *Specific Populations (8.1)*].

216 Infertility:

217 Males

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

221 **8.7 Hepatic Impairment**

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

228 **8.8 Renal Impairment**

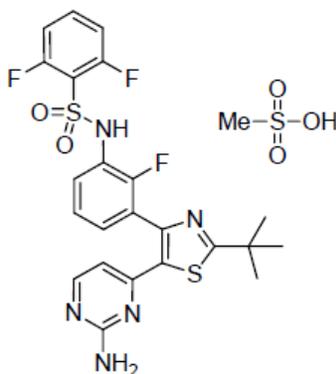
229 No formal pharmacokinetic trial in patients with renal impairment has been conducted. Dose
230 adjustment is not recommended for patients with mild or moderate renal impairment based on
231 the results of the population pharmacokinetic analysis. An appropriate dose has not been
232 established for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

233 **10 OVERDOSAGE**

234 There is no information on overdosage of TAFINLAR.

235 **11 DESCRIPTION**

236 Dabrafenib mesylate is a kinase inhibitor. The chemical name for dabrafenib mesylate is N-
237 [5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2,6-
238 difluorophenyl sulfonamide, methanesulfonate salt. It has the molecular formula
239 $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$ and a molecular weight of 615.68. Dabrafenib mesylate has the
240 following chemical structure.



241
242
243 Dabrafenib mesylate is a white to slightly colored solid with three pK_a s: 6.6, 2.2, and -1.5. It is
244 very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.
245 TAFINLAR (dabrafenib) capsules are supplied as 50 mg and 75 mg capsules for oral
246 administration. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg
247 of dabrafenib free base. Each 75 mg capsule contains 88.88 mg dabrafenib mesylate equivalent
248 to 75 mg of dabrafenib free base.

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

252 **12 CLINICAL PHARMACOLOGY**

253 **12.1 Mechanism of Action**

254 Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC_{50} values of
255 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes,
256 respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC_{50} values of 3.2
257 and 5.0 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher
258 concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E,
259 can result in constitutively activated BRAF kinases that may stimulate tumor cell growth [*see*
260 *Indications and Usage (1)*]. Dabrafenib inhibits BRAF V600 mutation-positive melanoma cell
261 growth in vitro and in vivo.

262 **12.3 Pharmacokinetics**

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

269 Administration of dabrafenib with a high-fat meal decreased C_{max} by 51%, decreased AUC by
270 31%, and delayed median T_{max} by 3.6 hours as compared to the fasted state [*see Dosage and*
271 *Administration (2.2)*].

272 **Distribution:** Dabrafenib is 99.7% bound to human plasma proteins. The apparent volume of
273 distribution (V_d/F) is 70.3 L.

274 **Metabolism:** The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to
275 form hydroxy-dabrafenib. Hydroxy-dabrafenib is further oxidized via CYP3A4 to form carboxy-
276 dabrafenib and subsequently excreted in bile and urine. Carboxy-dabrafenib is decarboxylated to
277 form desmethyl-dabrafenib; desmethyl-dabrafenib may be reabsorbed from the gut. Desmethyl-
278 dabrafenib is further metabolized by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib
279 terminal half-life (10 hours) parallels that of dabrafenib while the carboxy- and desmethyl-
280 dabrafenib metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite-to-parent
281 AUC ratios following repeat-dose administration are 0.9, 11, and 0.7 for hydroxy-, carboxy-, and
282 desmethyl-dabrafenib, respectively. Based on systemic exposure, relative potency, and
283 pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to
284 the clinical activity of dabrafenib.

285 **Elimination:** The mean terminal half-life of dabrafenib is 8 hours after oral administration. The
286 apparent clearance of dabrafenib is 17.0 L/h after single dosing and 34.4 L/h after 2 weeks of
287 twice-daily dosing.

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

290 **Specific Populations:**

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

294 **Pediatric:** Pharmacokinetics of dabrafenib have not been studied in pediatric patients.

295 **Renal:** No formal pharmacokinetic trial in patients with renal impairment has been conducted.
296 The pharmacokinetics of dabrafenib were evaluated using a population analysis in 233 patients
297 with mild renal impairment (GFR 60 to 89 mL/min/1.73 m²) and 30 patients with moderate renal

298 impairment (GFR 30 to 59 mL/min/1.73 m²) enrolled in clinical trials. Mild or moderate renal
299 impairment has no effect on systemic exposure to dabrafenib and its metabolites. No data are
300 available in patients with severe renal impairment.

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

306 Drug Interactions:

307 Human liver microsome studies show that dabrafenib is a substrate of CYP3A4 and CYP2C8
308 while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Dabrafenib is a
309 substrate of human P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) in vitro.

310 In human hepatocytes, dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4
311 mRNA levels up to 32 times the control levels and is a moderate inducer of CYP3A4 in vivo. In
312 a clinical trial in 12 subjects following coadministration of repeat doses of dabrafenib and a
313 single dose of midazolam (a CYP3A4 substrate), midazolam C_{max} and AUC_(0-∞) were decreased
314 61% and 74%, respectively. Dabrafenib is a moderate inducer of CYP3A4 and may induce other
315 enzymes such as CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UDP glucuronosyltransferases
316 (UGT) and may induce transporters.

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

321

322 **13 NONCLINICAL TOXICOLOGY**

323 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

337 **13.2 Animal Toxicology and/or Pharmacology**

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

343 **14 CLINICAL STUDIES**

344 In Trial 1, the safety and efficacy of TAFINLAR were demonstrated in an international, multi-
345 center, randomized (3:1), open-label, active-controlled trial conducted in 250 patients with
346 previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma.
347 Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. Patients were
348 randomized to receive TAFINLAR 150 mg by mouth twice daily (n = 187) or dacarbazine 1,000
349 mg/m² intravenously every 3 weeks (n = 63). Randomization was stratified by disease stage at
350 baseline [unresectable stage III (regional nodal or in-transit metastases), M1a (distant skin,
351 subcutaneous, or nodal metastases), or M1b (lung metastases) vs. M1c melanoma (all other
352 visceral metastases or elevated serum LDH)]. The main efficacy outcome measure was
353 progression-free survival (PFS) as assessed by the investigator. In addition, an independent
354 radiology review committee (IRRC) assessed the following efficacy outcome measures in pre-
355 specified supportive analyses: PFS, confirmed objective response rate (ORR), and duration of
356 response.

357 The median age of patients in Trial 1 was 52 years. The majority of the trial population was male
358 (60%), white (99%), had an ECOG performance status of 0 (67%), M1c disease (66%), and
359 normal LDH (62%). All patients had tumor tissue with mutations in BRAF V600E as determined
360 by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were
361 tested retrospectively, using an FDA-approved companion diagnostic test, THxID™-BRAF
362 assay.

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

366 Trial 1 demonstrated a statistically significant increase in progression-free survival in the patients
367 treated with TAFINLAR. Table 5 and Figure 1 summarize the PFS results.

368

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

	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 (95% CI)	52% (44, 59)	17% (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)

371 ^a Pike estimator, stratified by disease state.

372 ^b Stratified log-rank test.

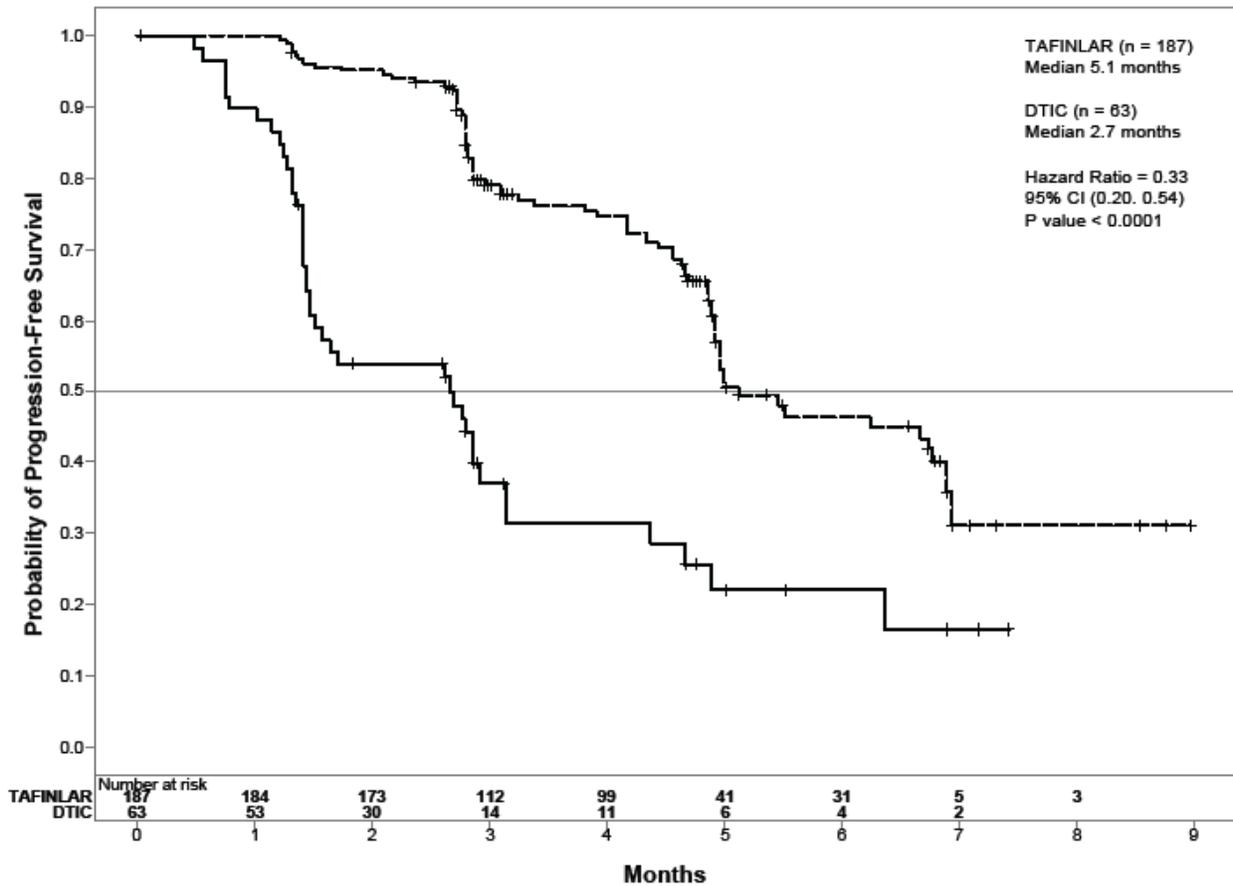
373 CI = Confidence interval; CR = complete response; HR = hazard ratio; NR = not reached; PR =
 374 partial response

375

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377

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



378

379

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

383

384 The activity of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma,
385 metastatic to the brain was evaluated in a single arm, open-label, two-cohort, multi-center trial
386 (Trial 2). All patients received TAFINLAR 150 mg twice daily. Patients in Cohort A (n=74)
387 had received no prior local therapy for brain metastases, while patients in Cohort B (n=65) had
388 received at least one local therapy for brain metastases, including, but not limited to, surgical
389 resection, whole brain radiotherapy, or stereotactic radiosurgery such as gamma knife, linear-
390 accelerated-based radiosurgery, charged particles, or CyberKnife. In addition, patients in Cohort
391 B were required to have evidence of disease progression in a previously treated lesion or an
392 untreated lesion. Additional eligibility criteria were at least one measurable lesion of 0.5 cm or
393 greater in largest diameter on contrast-enhanced MRI, stable or decreasing corticosteroid dose,

394 and no more than two prior systemic regimens for treatment of metastatic disease. The primary
 395 outcome measure was estimation of the overall intracranial response rate (OIRR) in each cohort.
 396 The median age of patients in Cohort A was 50 years, 72% were male, 100% were white, 59%
 397 had a pre-treatment ECOG performance status of 0, and 57% had an elevated LDH value at
 398 baseline. The median age of patients in Cohort B was 51 years, 63% were male, 98% were
 399 white, 66% had a pre-treatment ECOG performance status of 0, and 54% had an elevated LDH
 400 value at baseline. Efficacy results as determined by an independent radiology review committee,
 401 masked to investigator response assessments, are provided in Table 6.

402
 403 **Table 6. Efficacy Results in Patients with BRAF V600E Melanoma Brain Metastases (Trial**
 404 **2)**

Endpoint	IRRC Assessed Response	
	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)

405 IRRC = Independent radiology review committee; CI = Confidence interval; NR = not reached

406 **16 HOW SUPPLIED/STORAGE AND HANDLING**

407 50 mg Capsules: Dark red capsule imprinted with ‘GS TEW’ and ‘50 mg’ available in bottles of
 408 120 (NDC 0173-0846-08). Each bottle contains a silica gel desiccant.

409 75 mg Capsules: Dark pink capsule imprinted with ‘GS LHF’ and ‘75 mg’ available in bottles of
 410 120 (NDC 0173-0847-08). Each bottle contains a silica gel desiccant.

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

413 **17 PATIENT COUNSELING INFORMATION**

414 See FDA-approved patient labeling (Medication Guide).

415 Inform patients of the following:

- 416 • Evidence of BRAF V600E mutation in the tumor specimen is necessary to identify patients
 417 for whom treatment with TAFINLAR is indicated [see *Dosage and Administration (2.1)*].

- 418 • TAFINLAR increases the risk of developing new primary cutaneous malignancies. Advise
419 patients to contact their doctor immediately for any new lesions or changes to existing lesions
420 on their skin [see Warnings and Precautions (5.1)].
- 421 • TAFINLAR causes pyrexia including serious febrile drug reactions. Instruct patients to
422 contact their doctor if they experience a fever while taking TAFINLAR [see Warnings and
423 Precautions (5.3)].
- 424 • TAFINLAR can impair glucose control in diabetic patients resulting in the need for more
425 intensive hypoglycemic treatment. Advise patients to contact their doctor to report symptoms
426 of severe hyperglycemia [see Warnings and Precautions (5.4)].
- 427 • TAFINLAR may cause hemolytic anemia in patients with glucose-6-phosphate
428 dehydrogenase (G6PD) deficiency. Advise patients with known G6PD deficiency to contact
429 their doctor to report signs or symptoms of anemia or hemolysis [see Warnings and
430 Precautions (5.6)].
- 431 • TAFINLAR can cause fetal harm if taken during pregnancy. Instruct female patients to use
432 non-hormonal, highly effective contraception during treatment and for 4 weeks after
433 treatment. Advise patients to contact their doctor if they become pregnant, or if pregnancy is
434 suspected, while taking TAFINLAR [see Use in Specific Populations (8.1)].
- 435 • Nursing infants may experience serious adverse reactions if the mother is taking TAFINLAR
436 during breastfeeding. Advise breastfeeding mothers to discontinue nursing while taking
437 TAFINLAR [see Use in Specific Populations (8.3)].
- 438 • Male patients are at an increased risk for impaired spermatogenesis [see Use in Specific
439 Populations (8.6)].
- 440 • TAFINLAR should be taken either at least 1 hour before or at least 2 hours after a meal [see
441 Dosage and Administration (2.1)].

442

443 TAFINLAR is a registered trademark of GlaxoSmithKline.

444 THxID is a trademark of bioMérieux.

445



446

447 GlaxoSmithKline

448 Research Triangle Park, NC 27709

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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.

485 TAFINLAR is not used to treat people with a type of skin cancer called wild-type
486 BRAF melanoma.

487 It is not known if TAFINLAR is safe and effective in children.
488

489 **What should I tell my healthcare provider before taking TAFINLAR?**

490 **Before you start taking TAFINLAR, tell your healthcare provider if you:**

- 491 • have liver or kidney problems
- 492 • have diabetes
- 493 • plan to have surgery, dental, or other medical procedures
- 494 • have a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme
- 495 • have any other medical conditions
- 496 • are pregnant or plan to become pregnant. TAFINLAR can harm your unborn
497 baby.
 - 498 ○ Females who are able to become pregnant should use birth control during
499 treatment and for 4 weeks after stopping TAFINLAR.
 - 500 ○ Birth control using hormones (such as birth control pills, injections, or
501 patches) may not work as well while you are taking TAFINLAR. You should
502 use another effective method of birth control while taking TAFINLAR. Talk
503 to your healthcare provider about birth control methods that may be right
504 for you.
 - 505 ○ Tell your healthcare provider right away if you become pregnant during
506 treatment with TAFINLAR.
- 507 • are breastfeeding or plan to breastfeed. It is not known if TAFINLAR passes into
508 your breast milk. You and your healthcare provider should decide if you will take
509 TAFINLAR or breastfeed. You should not do both.

510

511 TAFINLAR may cause lower sperm counts in men. This could affect the ability to
512 father a child. Talk to your healthcare provider if this is a concern for you. Talk to
513 your healthcare provider about family planning options that might be right for you.
514

515 **Tell your healthcare provider about all the medicines you take** including
516 prescription and over-the-counter medicines, vitamins, and herbal supplements.
517 TAFINLAR and certain other medicines can affect each other, causing side effects.
518 TAFINLAR may affect the way other medicines work, and other medicines may

519 affect how TAFINLAR works. You can ask your pharmacist for a list of medicines
520 that may interact with TAFINLAR.

521

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

524

525 **How should I take TAFINLAR?**

526 • Take TAFINLAR exactly as your healthcare provider tells you. Do not change
527 your dose or stop TAFINLAR unless your healthcare provider tells you.

528 • Take TAFINLAR 2 times a day, about 12 hours apart.

529 • Take TAFINLAR at least 1 hour before or 2 hours after a meal.

530 • Do not open, crush, or break TAFINLAR capsules.

531 • If you miss a dose, take it as soon as you remember. If it is within 6 hours of
532 your next scheduled dose, just take your next dose at your regular time. Do not
533 make up for the missed dose. If you take too much TAFINLAR, call your
534 healthcare provider or go to the nearest hospital emergency room right away.

535

536 **What are the possible side effects of TAFINLAR?**

537 **TAFINLAR may cause serious side effects, including:**

538 • **See “What is the most important information I should know about**
539 **TAFINLAR?”**

540 • **Fever.** TAFINLAR can cause fever, including severe fever. In some cases, too
541 much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems
542 may happen with the fever. Tell your healthcare provider right away if you get a
543 fever while taking TAFINLAR.

544 • **Blood sugar problems.** Some people may develop high blood sugar or
545 worsening diabetes during treatment with TAFINLAR. If you are diabetic, your
546 healthcare provider will check your blood sugar levels before and during
547 treatment with TAFINLAR. Tell your healthcare provider if you have any of the
548 following symptoms of high blood sugar:

549 o increased thirst

550 o urinating more often than normal

551 o your breath smells like fruit

552

553 • **Eye problems.** You should have your eyes examined before and while you are
554 taking TAFINLAR. Tell your healthcare provider right away if you get these
555 symptoms during treatment with TAFINLAR:

556 o eye pain, swelling, or redness

557 o blurred vision or other vision changes during treatment with TAFINLAR

558

559 The most common side effects of TAFINLAR include:

560 • thickening of the outer layers of
561 the skin

562 • headache

563 • joint aches

564 • warts

565 • hair loss

566 • redness, swelling, peeling, or

567 tenderness of hands or feet

568

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

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

573 Call your doctor for medical advice about side effects. You may report side effects
574 to FDA at 1-800-FDA-1088. You may also report side effects to GSK at 1-888-825-
575 5249.

576

577 **How should I store TAFINLAR?**

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

579 • Ask your healthcare provider or pharmacist how to safely throw away TAFINLAR
580 that is out of date or no longer needed.

581

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

583

584 **General information about TAFINLAR**

585 Medicines are sometimes prescribed for purposes other than those listed in a
586 Medication Guide. Do not use TAFINLAR for a condition for which it was not
587 prescribed. Do not give TAFINLAR to other people, even if they have the same
588 symptoms that you have. It may harm them.

589 If you would like more information, talk with your healthcare provider. You can ask
590 your healthcare provider or pharmacist for information about TAFINLAR that is
591 written for health professionals.

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

594

595 **What are the ingredients in TAFINLAR?**

596 Active ingredient: dabrafenib

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

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

601

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

604

605 TAFINLAR is a registered trademark of GlaxoSmithKline.

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609 Research Triangle Park, NC 27709

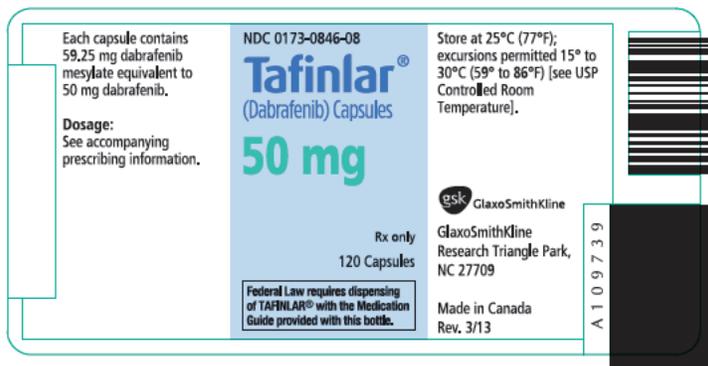
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613 Issued: May 2013

614 TFR: 1MG



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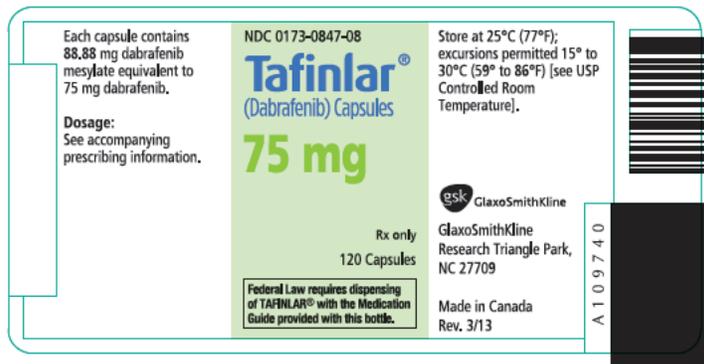
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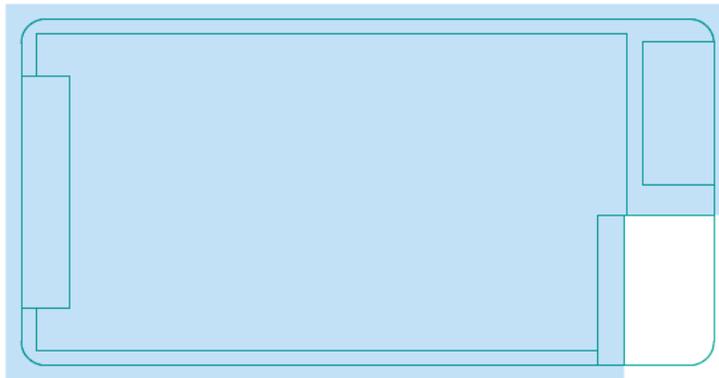
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RICHARD PAZDUR
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