

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204114Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MEKINIST (trametinib) tablets, for oral use

Initial U.S. Approval: 2013

INDICATIONS AND USAGE

MEKINIST is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1)

Limitation of use: MEKINIST is not indicated for the treatment of patients who have received prior BRAF inhibitor therapy. (1)

DOSAGE AND ADMINISTRATION

- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with MEKINIST. (2.1)
- The recommended dose is 2 mg orally once daily taken at least 1 hour before or at least 2 hours after a meal. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.5 mg, 1 mg, and 2 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Cardiomyopathy: Re-assess LVEF after one month of treatment, and evaluate approximately every 2 to 3 months thereafter. (5.1)

- Retinal Pigment Epithelial Detachment (RPED): Perform ophthalmologic evaluation for any visual disturbances. Withhold MEKINIST if RPED is diagnosed and discontinue if no improvement after 3 weeks. (5.2)
- Retinal Vein Occlusion (RVO): Discontinue MEKINIST. (5.3)
- Interstitial Lung Disease (ILD): Withhold MEKINIST for new or progressive unexplained pulmonary symptoms or findings, such as cough, dyspnea, hypoxia, or infiltrates. Permanently discontinue MEKINIST for treatment-related ILD or pneumonitis. (5.4)
- Serious Skin Toxicity: Monitor for skin toxicities and for secondary infections. Discontinue for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of MEKINIST. (5.5)
- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus. (5.6, 8.1, 8.6)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 20\%$) for MEKINIST include rash, diarrhea, and lymphedema. (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.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Females and Males of Reproductive Potential: Counsel female patients on pregnancy planning and prevention. May impair fertility. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection
- 2.2 Recommended Dosing
- 2.3 Dose Modifications

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Cardiomyopathy
- 5.2 Retinal Pigment Epithelial Detachment (RPED)
- 5.3 Retinal Vein Occlusion (RVO)
- 5.4 Interstitial Lung Disease
- 5.5 Serious Skin Toxicity
- 5.6 Embryofetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Females and Males of Reproductive Potential

8.7 Hepatic Impairment

8.8 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 BRAF V600E or V600K Mutation-Positive Metastatic Melanoma
- 14.2 Lack of Clinical Activity in Metastatic Melanoma Following BRAF Inhibitor Therapy

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 MEKINIST™ is indicated for the treatment of patients with unresectable or metastatic melanoma
4 with BRAF V600E or V600K mutations, as detected by an FDA-approved test [*see Clinical*
5 *Studies (14.1)*].

6 **Limitation of use:** MEKINIST is not indicated for treatment of patients who have received prior
7 BRAF-inhibitor therapy [*see Clinical Studies (14.2)*].

8 **2 DOSAGE AND ADMINISTRATION**

9 **2.1 Patient Selection**

10 Select patients for treatment of unresectable or metastatic melanoma with MEKINIST based on
11 presence of BRAF V600E or V600K mutation in tumor specimens [*see Clinical Studies (14.1)*].
12 Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is
13 available at: <http://www.fda.gov/CompanionDiagnostics>.

14 **2.2 Recommended Dosing**

15 The recommended dose is 2 mg orally once daily until disease progression or unacceptable
16 toxicity. Take at least 1 hour before or 2 hours after a meal. Do not take a missed dose within
17 12 hours of the next dose.

18 **2.3 Dose Modifications**19 **Table 1. Recommended Dose Modifications for MEKINIST**

Target Organ	Adverse Reaction^a	Dose Modification
<i>Cutaneous</i>	Grade 2 rash	Reduce dose of MEKINIST by 0.5 mg <u>or</u> discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Intolerable Grade 2 rash that does not improve within 3 weeks following dose reduction Grade 3 or 4 rash	Withhold MEKINIST for up to 3 weeks If improved within 3 weeks, resume MEKINIST at a lower dose (reduced by 0.5 mg) <u>or</u> discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Intolerable Grade 2 or Grade 3 or 4 rash that does not improve within 3 weeks despite interruption of MEKINIST dosing	Permanently discontinue MEKINIST
<i>Cardiac</i>	Asymptomatic, absolute decrease in LVEF of 10% <u>or</u> greater from baseline <u>and</u> is below institutional lower limits of normal (LLN) from pretreatment value	Withhold MEKINIST for up to 4 weeks
	Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline <u>and</u> is below LLN that improves to normal LVEF value within 4 weeks following interruption of MEKINIST	If improved within 4 weeks, resume MEKINIST at a lower dose (reduced by 0.5 mg) <u>or</u> discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Symptomatic congestive heart failure Absolute decrease in LVEF of greater than 20% from baseline that is below LLN Absolute decrease in LVEF of 10% <u>or</u> greater from baseline and is below LLN that does not improve to normal LVEF value within 4 weeks following interruption of MEKINIST	Permanently discontinue MEKINIST
<i>Ocular</i>	Grade 2-3 retinal pigment epithelial detachments (RPED)	Withhold MEKINIST for up to 3 weeks
	Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	If improved within 3 weeks, resume MEKINIST at a lower dose (reduced by 0.5 mg) <u>or</u> discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Retinal vein occlusion Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue MEKINIST
<i>Pulmonary</i>	Interstitial lung disease/pneumonitis	Permanently discontinue MEKINIST
<i>Other</i>	Grade 3 adverse reaction	Withhold MEKINIST for up to 3 weeks
	If Grade 3 adverse reaction improves to Grade 0-1 following interruption of MEKINIST within 3 weeks	Reduce dose of MEKINIST by 0.5 mg <u>or</u> discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Grade 4 adverse reaction Grade 3 adverse reaction that does not improve to Grade 0-1 within 3 weeks	Permanently discontinue MEKINIST

20 ^a Note: The intensity of clinical adverse events graded by the National Cancer Institute Common Terminology
21 Criteria for Adverse Events (CTCAE) version 4.0.

22 **3 DOSAGE FORMS AND STRENGTHS**

23 0.5 mg Tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one
24 face and ‘TFC’ on the opposing face.

25 1 mg Tablets: White, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and
26 ‘LHE’ on the opposing face.

27 2 mg Tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and
28 ‘HMJ’ on the opposing face.

29 **4 CONTRAINDICATIONS**

30 None.

31 **5 WARNINGS AND PRECAUTIONS**

32 **5.1 Cardiomyopathy**

33 In Trial 1, cardiomyopathy [defined as cardiac failure, left ventricular dysfunction, or decreased
34 left ventricular ejection fraction (LVEF)] occurred in 7% (14/211) of patients treated with
35 MEKINIST; no chemotherapy-treated patient in Trial 1 developed cardiomyopathy. The median
36 time to onset of cardiomyopathy in patients treated with MEKINIST was 63 days (range 16 to
37 156 days); cardiomyopathy was identified within the first month of treatment with MEKINIST in
38 five of these 14 patients. Four percent of patients in Trial 1 required discontinuation (4/211)
39 and/or dose reduction (7/211) of MEKINIST. Cardiomyopathy resolved in 10 of these 14 (71%)
40 patients.

41 Across clinical trials of MEKINIST at the recommended dose (N = 329), 11% of patients
42 developed evidence of cardiomyopathy (decrease in LVEF below institutional lower limits of
43 normal with an absolute decrease in LVEF \geq 10% below baseline) and 5% demonstrated a
44 decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF
45 of \geq 20% below baseline.

46 Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of
47 MEKINIST, one month after initiation of MEKINIST, and then at 2- to 3-month intervals while
48 on treatment. Withhold treatment if absolute LVEF value decreases by 10% from pre-treatment
49 values and is less than the lower limit of normal. Permanently discontinue MEKINIST for
50 symptomatic cardiomyopathy or persistent, asymptomatic LVEF dysfunction that does not
51 resolve within 4 weeks [*see Dosage and Administration (2.3)*].

52 **5.2 Retinal Pigment Epithelial Detachment (RPED)**

53 Retinal pigment epithelial detachments (RPED) can occur during treatment with MEKINIST. In
54 Trial 1, where ophthalmologic examinations including retinal evaluation were performed
55 pretreatment and at regular intervals during treatment, one patient (0.5%) receiving MEKINIST
56 developed RPED and no cases of RPED were identified in chemotherapy-treated patients.

57 Across all clinical trials of MEKINIST, the incidence of RPED was 0.8% (14/1749).

58 Retinal detachments were often bilateral and multifocal, occurring in the macular region of the
59 retina. RPED led to reduction in visual acuity that resolved after a median of 11.5 days (range: 3
60 to 71 days) following the interruption of dosing with MEKINIST, although Ocular Coherence
61 Tomography (OCT) abnormalities persisted beyond a month in at least several cases.

62 Perform ophthalmological evaluation at any time a patient reports visual disturbances and
63 compare to baseline, if available. Withhold MEKINIST if RPED is diagnosed. If resolution of
64 the RPED is documented on repeat ophthalmological evaluation within 3 weeks, resume
65 MEKINIST at a reduced dose [*see Dosage and Administration (2.3)*].

66 **5.3 Retinal Vein Occlusion (RVO)**

67 Across all clinical trials of MEKINIST, the incidence of RVO was 0.2% (4/1749). An RVO may
68 lead to macular edema, decreased visual function, neovascularization, and glaucoma.

69 Urgently (within 24 hours) perform ophthalmological evaluation for patient-reported loss of
70 vision or other visual disturbances. Permanently discontinue MEKINIST in patients with
71 documented retinal vein occlusion [*see Dosage and Administration (2.3)*].

72 **5.4 Interstitial Lung Disease**

73 In clinical trials of MEKINIST at the recommended dose (N = 329), interstitial lung disease
74 (ILD) or pneumonitis occurred in 1.8% of patients. In Trial 1, 2.4% (5/211) of patients treated
75 with MEKINIST developed ILD or pneumonitis; all five patients required hospitalization. The
76 median time to first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days).

77 Withhold MEKINIST in patients presenting with new or progressive pulmonary symptoms and
78 findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical
79 investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-
80 related ILD or pneumonitis.

81 **5.5 Serious Skin Toxicity**

82 In Trial 1, the overall incidence of skin toxicity including rash, dermatitis, acneiform rash,
83 palmar-plantar erythrodysesthesia syndrome, and erythema was 87% in patients treated with
84 MEKINIST and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of
85 patients treated with MEKINIST. Skin toxicity requiring hospitalization occurred in 6% of
86 patients treated with MEKINIST, most commonly for secondary infections of the skin requiring
87 intravenous antibiotics or severe skin toxicity without secondary infection. In comparison, no

88 patients treated with chemotherapy required hospitalization for severe skin toxicity or infections
89 of the skin. The median time to onset of skin toxicity in patients treated with MEKINIST was 15
90 days (range: 1 to 221 days) and median time to resolution of skin toxicity was 48 days (range: 1
91 to 282 days). Reductions in the dose of MEKINIST were required in 12% and permanent
92 discontinuation of MEKINIST was required in 1% of patients with skin toxicity.

93 Monitor patients receiving MEKINIST for skin toxicities and for secondary infections [*see*
94 *Dosage and Administration (2.3)*].

95 **5.6 Embryofetal Toxicity**

96 Based on its mechanism of action, MEKINIST can cause fetal harm when administered to a
97 pregnant woman. MEKINIST was embryotoxic and abortifacient in rabbits at doses greater than
98 or equal to those resulting in exposures approximately 0.3 times the human exposure at the
99 recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes
100 pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.
101 [*See Use in Specific Populations (8.1)*].

102 Advise female patients of reproductive potential to use highly effective contraception during
103 treatment with MEKINIST and for 4 months after treatment. Advise patients to contact their
104 healthcare provider if they become pregnant, or if pregnancy is suspected, while taking
105 MEKINIST. [*See Use in Specific Populations (8.1), (8.6)*].

106 **6 ADVERSE REACTIONS**

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

- 108 • Cardiomyopathy [*see Warnings and Precautions (5.1)*]
- 109 • Retinal pigment epithelial detachment [*see Warnings and Precautions (5.2)*]
- 110 • Retinal vein occlusion [*see Warnings and Precautions (5.3)*]
- 111 • Interstitial lung disease [*see Warnings and Precautions (5.4)*]
- 112 • Serious skin toxicity [*see Warnings and Precautions (5.5)*]

113 **6.1 Clinical Trials Experience**

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

117 The data described in the Warnings and Precautions section and below reflect exposure to
118 MEKINIST in 329 patients including 107 (33%) exposed for greater than or equal to 6 months
119 and 30 (9%) exposed for greater than or equal to one year. MEKINIST was studied in open-label
120 single-arm trials (N = 118) or in an open-label, randomized, active-controlled trial (N = 211).
121 The median age was 54, 60% were male, >99% were white, and all patients had metastatic

122 melanoma. All patients received 2 mg once daily doses of MEKINIST. The incidence of RPED
 123 and RVO are obtained from the 1,749 patients from all clinical trials with MEKINIST.

124 Table 2 presents adverse reactions identified from analyses of Trial 1, [see *Clinical Studies*
 125 (14.1)] a randomized open-label trial of patients with BRAF V600E or V600K mutation-positive
 126 melanoma receiving MEKINIST (N = 211) 2 mg orally once daily or chemotherapy (N = 99)
 127 [either dacarbazine 1,000 mg/m² every 3 weeks or paclitaxel 175 mg/m² every 3 weeks]. Patients
 128 with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence
 129 of Class II or greater congestive heart failure (New York Heart Association) were excluded from
 130 Trial 1. The median duration of treatment with MEKINIST was 4.3 months. In Trial 1, 9% of
 131 patients receiving MEKINIST experienced adverse reactions resulting in permanent
 132 discontinuation of trial medication. The most common adverse reactions resulting in permanent
 133 discontinuation of MEKINIST were decreased left ventricular ejection fraction (LVEF),
 134 pneumonitis, renal failure, diarrhea, and rash. Adverse reactions led to dose reductions in 27% of
 135 patients treated with MEKINIST. Rash and decreased LVEF were the most common reasons
 136 cited for dose reductions of MEKINIST.

137
 138 **Table 2. Selected Adverse Reactions Occurring in ≥10% of Patients Receiving MEKINIST**
 139 **and at a Higher Incidence than in the Control Arm^a**

Adverse Reactions	MEKINIST (N = 211)		Chemotherapy (N = 99)	
	All Grades ^b	Grades 3 and 4 ^c	All Grades ^b	Grades 3 and 4 ^c
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritus	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis ^d	15	2	2	0
Abdominal pain ^e	13	1	5	1
Vascular disorders				
Lymphedema ^f	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage ^g	13	<1	0	0

140 ^a Events included are higher in the trametinib arm compared with chemotherapy by ≥5% in
 141 overall incidence or by ≥2% Grade 3-4 adverse reactions higher in trametinib arm compared
 142 with chemotherapy.

- 143 ^b National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
 144 ^c Grade 4 adverse reactions were limited to rash (n = 1) in trametinib arm and diarrhea (n = 1)
 145 in the chemotherapy arm.
 146 ^d Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, and mucosal
 147 inflammation.
 148 ^e Includes the following terms: abdominal pain, abdominal pain lower, abdominal pain upper,
 149 and abdominal tenderness.
 150 ^f Includes the following terms: lymphedema, edema, and peripheral edema.
 151 ^g Includes the following terms: epistaxis, gingival bleeding, hematochezia, rectal hemorrhage,
 152 melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, and conjunctival
 153 hemorrhage.

154 Other clinically important adverse reactions observed in ≤10% of patients (N = 329) treated with
 155 MEKINIST were:

156 Nervous System Disorders: Dizziness, dysgeusia.

157 Ocular Disorders: Vision blurred, dry eye.

158 Infections and Infestations: Folliculitis, rash pustular, cellulitis.

159 Cardiac Disorders: Bradycardia.

160 Gastrointestinal Disorders: Xerostomia.

161 Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis

162

163 **Table 3. Percent-Patient Incidence of Laboratory Abnormalities Occurring at a Higher**
 164 **Incidence in Patients Treated With MEKINIST in Trial 1 [Between Arm Difference of**
 165 **≥5% (All Grades) or ≥2% (Grades 3 or 4)^a**

Preferred Term	MEKINIST (N = 211)		Chemotherapy (N = 99)	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Increased Aspartate aminotransferase (AST)	60	2	16	1
Increased Alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased Alkaline phosphatase	24	2	18	3

166 ^a No Grade 4 events were reported in either treatment arm.

167 **7 DRUG INTERACTIONS**

168 No formal clinical studies have been conducted to evaluate human cytochrome P450 (CYP)
 169 enzyme-mediated drug interactions with trametinib [see *Clinical Pharmacology (12.3)*].

170 **8 USE IN SPECIFIC POPULATIONS**

171 **8.1 Pregnancy**

172 Pregnancy Category D

173 **Risk Summary:** MEKINIST can cause fetal harm when administered to a pregnant woman.
174 Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those
175 resulting in exposures approximately 0.3 times the human exposure at the recommended clinical
176 dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this
177 drug, the patient should be apprised of the potential hazard to the fetus [*see Warnings and*
178 *Precautions (5.6)*].

179 **Animal Data:** In reproductive toxicity studies, administration of trametinib to rats during the
180 period of organogenesis resulted in decreased fetal weights at doses greater than or equal to
181 0.031 mg/kg/day (approximately 0.3 times the human exposure based on AUC at the
182 recommended dose). In rats, at a dose resulting in exposures 1.8 fold higher than the human
183 exposure at the recommended dose, there was maternal toxicity and an increase in post-
184 implantation loss.

185 In pregnant rabbits, administration of trametinib during the period of organogenesis resulted in
186 decreased fetal body weight and increased incidence of variations in ossification at doses greater
187 than or equal to 0.039 mg/kg/day (approximately 0.08 times the human exposure at the
188 recommended dose based on AUC). In rabbits administered trametinib at 0.15 mg/kg/day
189 (approximately 0.3 times the human exposure at the recommended dose based on AUC) there
190 was an increase in post-implantation loss, including total loss of pregnancy, compared to control
191 animals.

192 **8.3 Nursing Mothers**

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

197 **8.4 Pediatric Use**

198 The safety and effectiveness of MEKINIST have not been established in pediatric patients.

199 **8.5 Geriatric Use**

200 Clinical studies of MEKINIST did not include sufficient numbers of subjects aged 65 and over to
201 determine whether they respond differently from younger subjects. In Trial 1, 49 patients (23%)
202 were 65 years of age and older, and 9 patients (4%) were 75 years of age and older.

203 **8.6 Females and Males of Reproductive Potential**

204 Contraception: *Females*

205 MEKINIST can cause fetal harm when administered during pregnancy. Advise female patients
206 of reproductive potential to use highly effective contraception during treatment and for 4 months
207 after treatment. Advise patients to contact their healthcare provider if they become pregnant, or if
208 pregnancy is suspected, while taking MEKINIST [see *Use in Specific Populations (8.1)*].

209 Infertility: *Females*

210 Trametinib may impair fertility in female patients [see *Nonclinical Toxicology (13.1)*].

211

212 **8.7 Hepatic Impairment**

213 No formal clinical study has been conducted to evaluate the effect of hepatic impairment on the
214 pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild
215 hepatic impairment based on a population pharmacokinetic analysis [see *Clinical Pharmacology*
216 *(12.3)*].

217 The appropriate dose of MEKINIST has not been established in patients with moderate or severe
218 hepatic impairment.

219 **8.8 Renal Impairment**

220 No formal clinical study has been conducted to evaluate the effect of renal impairment on the
221 pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild or
222 moderate renal impairment based on a population pharmacokinetic analysis [see *Clinical*
223 *Pharmacology (12.3)*]. The appropriate dose of MEKINIST has not been established in patients
224 with severe renal impairment.

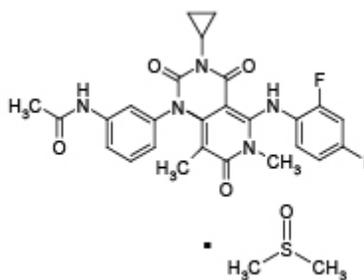
225 **10 OVERDOSAGE**

226 There were no reported cases of inadvertent overdosage with MEKINIST. The highest doses of
227 MEKINIST evaluated in clinical trials were 4 mg orally once daily and 10 mg administered
228 orally once daily on two consecutive days followed by 3 mg once daily. In seven patients treated
229 on one of these two schedules, there were two cases of retinal pigment epithelial detachments for
230 an incidence of 28%. Since trametinib is highly bound to plasma proteins, hemodialysis is likely
231 to be ineffective in the treatment of overdose with MEKINIST.

232 **11 DESCRIPTION**

233 Trametinib dimethyl sulfoxide is a kinase inhibitor. The chemical name is acetamide, N-[3-[3-
234 cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl- 2,4,7-
235 trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1).
236 It has a molecular formula $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ with a molecular mass of 693.53. Trametinib
237 dimethyl sulfoxide has the following chemical structure.

238



239
 240 Trametinib dimethyl sulfoxide is a white to almost white powder. It is practically insoluble in the
 241 pH range of 2 to 8 in aqueous media.

242 MEKINIST (trametinib) Tablets are supplied as 0.5-mg, 1-mg, and 2-mg tablets for oral
 243 administration. Each 0.5-mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent
 244 to 0.5 mg of trametinib non-solvated parent. Each 1-mg tablet contains 1.127 mg trametinib
 245 dimethyl sulfoxide equivalent to 1 mg of trametinib non-solvated parent. Each 2-mg tablet
 246 contains 2.254 mg trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib non-solvated
 247 parent.

248 The inactive ingredients of MEKINIST Tablets are: **Tablet Core:** mannitol, microcrystalline
 249 cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium
 250 lauryl sulfate, colloidal silicon dioxide. **Coating:** hypromellose, titanium dioxide, polyethylene
 251 glycol, polysorbate 80 (2-mg tablets), iron oxide yellow (0.5-mg tablets), iron oxide red (2-mg
 252 tablets).

253 **12 CLINICAL PHARMACOLOGY**

254 **12.1 Mechanism of Action**

255 Trametinib is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1
 256 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are
 257 upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes
 258 cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF
 259 pathway which includes MEK1 and MEK2. Trametinib inhibits BRAF V600 mutation-positive
 260 melanoma cell growth in vitro and in vivo.

261 **12.2 Pharmacodynamics**

262 Administration of 1 mg and 2 mg trametinib to patients with BRAF V600 mutation-positive
 263 melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of
 264 phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a
 265 marker of apoptosis).

266 **12.3 Pharmacokinetics**

267 The pharmacokinetics (PK) of trametinib were characterized following single- and repeat-oral
268 administration in patients with solid tumors and BRAF V600 mutation-positive metastatic
269 melanoma.

270 **Absorption:** After oral administration, the median time to achieve peak plasma concentrations
271 (T_{max}) is 1.5 hours post-dose. The mean absolute bioavailability of a single 2-mg oral dose of
272 trametinib tablet is 72%. The increase in C_{max} was dose proportional after a single dose of 0.125
273 to 10 mg while the increase in AUC was greater than dose-proportional. After repeat doses of
274 0.125 to 4 mg daily, both C_{max} and AUC increase proportionally with dose. Inter-subject
275 variability in AUC and C_{max} at steady state is 22% and 28%, respectively.

276 Administration of a single dose of trametinib with a high-fat, high-calorie meal decreased AUC
277 by 24%, C_{max} by 70% and delayed T_{max} by approximately 4 hours as compared to fasted
278 conditions [*see Dosage and Administration (2.2)*].

279 **Distribution:** Trametinib is 97.4% bound to human plasma proteins. The apparent volume of
280 distribution (V_d/F) is 214 L.

281 **Metabolism:** Trametinib is metabolized predominantly via deacetylation alone or with mono-
282 oxygenation or in combination with glucuronidation biotransformation pathways in vitro.
283 Deacetylation is likely mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases.
284 Following a single dose of [^{14}C]-trametinib, approximately 50% of circulating radioactivity is
285 represented as the parent compound. However, based on metabolite profiling after repeat dosing
286 of trametinib, $\geq 75\%$ of drug-related material in plasma is the parent compound.

287 **Elimination:** The estimated elimination half-life based on the population PK model is 3.9 to 4.8
288 days. The apparent clearance is 4.9 L/h.

289 Following oral administration of [^{14}C]-trametinib, $>80\%$ of excreted radioactivity was recovered
290 in the feces while $<20\%$ of excreted radioactivity was recovered in the urine with $<0.1\%$ of the
291 excreted dose as parent.

292 **Specific Populations:** Based on a population pharmacokinetic analysis, age, gender, and body
293 weight do not have a clinically important effect on the exposure of trametinib. There are
294 insufficient data to evaluate potential differences in the exposure of trametinib by race or
295 ethnicity.

296 **Hepatic Impairment:** Based on a population pharmacokinetic analysis in 64 patients with mild
297 hepatic impairment (total bilirubin \leq ULN and AST $>$ ULN or total bilirubin >1.0 - 1.5 x ULN and
298 any AST), mild hepatic impairment has no clinically important effect on the systemic exposure
299 of trametinib. The pharmacokinetics of trametinib have not been studied in patients with
300 moderate or severe hepatic impairment [*see Use in Specific Populations (8.7)*].

301 Renal Impairment: As renal excretion of trametinib is low (<20%), renal impairment is unlikely
302 to have a clinically important effect on the exposure of trametinib. Based on a population PK
303 analysis in 223 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 m²) and 35
304 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m²), mild and moderate
305 renal impairment have no clinically important effects on the systemic exposure of trametinib.
306 The PK of trametinib have not been studied in patients with severe renal impairment [*see Use in*
307 *Specific Populations (8.8)*].

308 Pediatrics: No studies have been conducted to evaluate the pharmacokinetics of trametinib in
309 pediatric patients.

310 Drug Interactions: No formal drug interaction studies have been conducted with trametinib.
311 Trametinib is not a substrate of CYP enzymes or efflux transporters P-gp or BCRP in vitro.

312 Based on in vitro studies, trametinib is not an inhibitor of CYP450 including CYP1A2, CYP2A6,
313 CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 or of transporters including OATP1B1,
314 OATP1B3, P-gp, and BCRP at a clinically relevant systemic concentration of 0.04 μM.
315 Trametinib is an inhibitor of CYP2C8 in vitro.

316 Trametinib is an inducer of CYP3A4 in vitro. Based on cross-study comparisons, oral
317 administration of trametinib 2 mg once daily with everolimus (sensitive CYP3A4 substrate)
318 5 mg once daily, had no clinically important effect on the AUC and C_{max} of everolimus.

319 **13 NONCLINICAL TOXICOLOGY**

320 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

321 Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic
322 in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells,
323 and micronuclei in the bone marrow of rats.

324 Trametinib may impair fertility in humans. In female rats given trametinib for up to 13 weeks,
325 increased follicular cysts and decreased corpora lutea were observed at doses ≥0.016 mg/kg/day
326 (approximately 0.3 times the human exposure at the recommended dose based on AUC). In rat
327 and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed on
328 male reproductive tissues [*see Use in Specific Populations (8.6)*].

329 **14 CLINICAL STUDIES**

330 **14.1 BRAF V600E or V600K Mutation-Positive Metastatic Melanoma**

331 The safety and efficacy of MEKINIST were evaluated in an international, multi-center,
332 randomized (2:1), open label, active-controlled trial (Trial 1) in 322 patients with BRAF V600E
333 or V600K mutation-positive, unresectable or metastatic melanoma. Patients were not permitted
334 to have more than one prior chemotherapy regimen for advanced or metastatic disease; prior
335 treatment with a BRAF inhibitor or MEK inhibitor was not permitted. The primary efficacy

336 outcome measure was progression-free survival (PFS). Patients were randomized to receive
337 MEKINIST 2 mg orally once daily (N = 214) or chemotherapy (N = 108) consisting of either
338 dacarbazine 1,000 mg/m² intravenously every 3 weeks or paclitaxel 175 mg/m² intravenously
339 every 3 weeks. Treatment continued until disease progression or unacceptable toxicity.
340 Randomization was stratified according to prior use of chemotherapy for advanced or metastatic
341 disease (yes versus no) and lactate dehydrogenase level (normal versus greater than upper limit
342 of normal). Tumor tissue was evaluated for BRAF mutations at a central testing site using a
343 clinical trial assay. Tumor samples from 289 patients (196 patients treated with MEKINIST and
344 93 chemotherapy-treated patients) were also tested retrospectively using an FDA-approved
345 companion diagnostic test, THxID™-BRAF assay.

346 The median age for randomized patients was 54 years, 54% were male, >99% were white, and
347 all patients had baseline ECOG performance status of 0 or 1. Most patients had metastatic
348 disease (94%), were Stage M1c (64%), had elevated LDH (36%), no history of brain metastasis
349 (97%), and received no prior chemotherapy for advanced or metastatic disease (66%). The
350 distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (<1%).
351 The median durations of follow-up prior to initiation of alternative treatment were 4.9 months for
352 patients treated with MEKINIST and 3.1 months for patients treated with chemotherapy. Fifty-
353 one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to
354 receive MEKINIST.

355 Trial 1 demonstrated a statistically significant increase in progression-free survival in the patients
356 treated with MEKINIST. Table 4 and Figure 1 summarize the PFS results.

357

358 **Table 4. Investigator-Assessed Progression-Free Survival and Confirmed Objective**
 359 **Response Results**

	MEKINIST N = 214	Chemotherapy N = 108
PFS		
Number of Events (%)	117 (55%)	77 (71%)
Progressive Disease	107 (50%)	70 (65%)
Death	10 (5%)	7 (6%)
Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR ^a (95% CI)	0.47 (0.34, 0.65)	
<i>P</i> value (log-rank test)	<i>P</i> <0.0001	
Confirmed Tumor Responses		
Objective Response Rate	22%	8%
(95% CI)	(17, 28)	(4, 15)
CR, n (%)	4 (2%)	0
PR, n (%)	43 (20%)	9 (8%)
Duration of Response		
Median, months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)

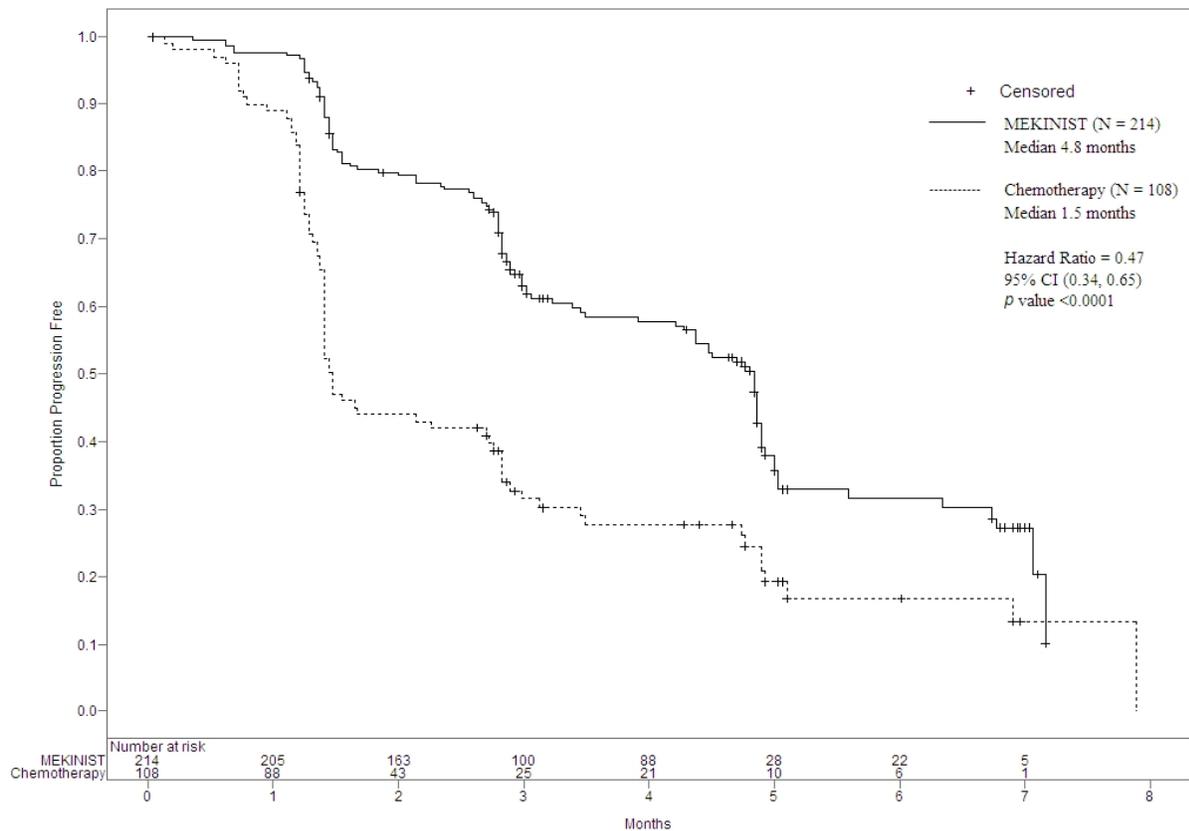
360 ^a Pike estimator.

361 CI = confidence interval; CR=complete response; HR = Hazard Ratio; NR=Not reached,

362 PFS = Progression-free Survival; PR=partial response.

363

364 **Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival (ITT**
365 **population)**



366
367

368 In supportive analyses based on independent radiologic review committee assessment, the PFS
369 results were consistent with those of the primary efficacy analysis.

370 **14.2 Lack of Clinical Activity in Metastatic Melanoma Following BRAF Inhibitor** 371 **Therapy**

372 The clinical activity of MEKINIST was evaluated in a single-arm, multicenter, international trial
373 (Trial 2) in 40 patients with BRAF V600E or V600K mutation-positive, unresectable or
374 metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients
375 received MEKINIST at a dose of 2 mg orally once daily until disease progression or
376 unacceptable toxicity.

377 The median age was 58 years, 63% were male, all were white, 98% had baseline ECOG PS of 0
378 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the
379 remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No

380 patient in Trial 2 achieved a confirmed partial or complete response as determined by the clinical
381 investigators.

382 **16 HOW SUPPLIED/STORAGE AND HANDLING**

383 0.5 mg Tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one
384 face and ‘TFC’ on the opposing face and are available in bottles of 30 (NDC 0173-0849-13).

385 1 mg Tablets: White, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and
386 ‘LHE’ on the opposing face and are available in bottles of 30 (NDC 0173-0858-13).

387 2 mg Tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and
388 ‘HMJ’ on the opposing face and are available in bottles of 30 (NDC 0173-0848-13).

389 Store refrigerated at 2° to 8°C (36° to 46°F). Do not freeze. Dispense in original bottle. Do not
390 remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

391 **17 PATIENT COUNSELING INFORMATION**

392 See FDA-approved patient labeling (Patient Information).

393 Inform patients of the following:

- 394 • Evidence of BRAF V600E or V600K mutation within the tumor specimen is necessary to
395 identify patients for whom treatment with MEKINIST is indicated [*see Dosage and*
396 *Administration (2.1)*].
- 397 • MEKINIST can cause cardiomyopathy. Advise patients to immediately report any signs or
398 symptoms of heart failure to their healthcare provider. [*See Warnings and Precautions (5.1)*.]
- 399 • MEKINIST causes severe visual disturbances that can lead to blindness. Advise patients to
400 contact their healthcare provider if they experience any changes in their vision. [*See*
401 *Warnings and Precautions (5.2, 5.3)*.]
- 402 • MEKINIST can cause interstitial lung disease (or pneumonitis). Advise patients to contact
403 their healthcare provider as soon as possible if they experience dyspnea. [*See Warnings and*
404 *Precautions (5.4)*.]
- 405 • MEKINIST often causes skin toxicities including acneiform rash. Advise patients to contact
406 their healthcare provider for progressive or intolerable rash. [*See Warnings and Precautions*
407 *(5.5)*.]
- 408 • MEKINIST causes hypertension. Advise patients that they need to undergo blood pressure
409 monitoring and to contact their healthcare provider if they develop symptoms of
410 hypertension.
- 411 • MEKINIST often causes diarrhea which may be severe in some cases. Inform patients of the
412 need to contact their healthcare provider if severe diarrhea occurs during treatment.
- 413 • MEKINIST should be taken at least 1 hour before or at least 2 hours after a meal.

- 414 • MEKINIST can cause fetal harm if taken during pregnancy. Instruct female patients to use
415 highly effective contraception during treatment and for 4 months after treatment. Advise
416 patients to contact their healthcare provider if they become pregnant, or if pregnancy is
417 suspected, while taking MEKINIST [*see Use in Specific Populations (8.1), (8.6)*].
418 • Nursing infants may experience serious adverse reactions if the mother is taking MEKINIST.
419 Advise lactating mothers to discontinue nursing while taking MEKINIST [*see Use in*
420 *Specific Populations (8.3)*].

421 MEKINIST is a trademark of GlaxoSmithKline.

422 THxID BRAF™ assay is a trademark of bioMerieux.



423

424 GlaxoSmithKline

425 Research Triangle Park, NC 27709

426 ©2013, GlaxoSmithKline. All rights reserved.

427 MKN:1PI

428 **Patient Information**
429 MEKINIST™ (MEK-in-ist)
430 (trametinib)
431 tablets

432 **What is MEKINIST?**

433 MEKINIST is a prescription medicine used to treat people with a type of skin cancer
434 called melanoma:

- 435 • that has spread to other parts of the body or cannot be removed by surgery,
436 and
- 437 • that has a certain type of abnormal “BRAF” gene

438 MEKINIST should not be used to treat people who have received a BRAF inhibitor
439 for treatment of their melanoma.

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

442 It is not known if MEKINIST is safe and effective in children.

443 **What should I tell my healthcare provider before taking MEKINIST?**

444 **Before you take MEKINIST, tell your healthcare provider if you:**

- 445 • have heart problems
- 446 • have lung or breathing problems
- 447 • have eye problems
- 448 • have high blood pressure (hypertension)
- 449 • have liver or kidney problems
- 450 • have any other medical conditions
- 451 • are pregnant or plan to become pregnant. MEKINIST can harm your unborn
452 baby.
 - 453 • Women who may become pregnant should use effective birth control
454 (contraception) during treatment with MEKINIST and for 4 months after
455 stopping treatment. Talk to your healthcare provider about birth control
456 methods that may be right for you. Tell your healthcare provider right away
457 if you become pregnant during treatment with MEKINIST.
- 458 • are breastfeeding or plan to breastfeed. It is not known if MEKINIST passes into
459 your breast milk. You and your healthcare provider should decide if you will take
460 MEKINIST or breastfeed. You should not do both.

461 **Tell your healthcare provider about all the medicines you take**, including
462 prescription and over-the-counter medicines, vitamins, and herbal supplements.

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

465 **How should I take MEKINIST?**

- 466 • Take MEKINIST exactly as your healthcare provider tells you to take it. Do not
467 change your dose or stop MEKINIST unless your healthcare provider tells you.
- 468 • Take MEKINIST one time a day.
- 469 • Take MEKINIST 1 hour before or 2 hours after meals.
- 470 • If you miss a dose, take it as soon as you remember. If it is within 12 hours of
471 your next scheduled dose, skip the missed dose. Just take the next dose at your
472 regular time.
- 473 • If you take too much MEKINIST, call your healthcare provider or go to the
474 nearest hospital emergency room right away.

475 **What are the possible side effects of MEKINIST?**

476 **MEKINIST may cause serious side effects, including:**

- 477 • **heart problems, including heart failure.** Your healthcare provider should
478 check your heart function before you start taking MEKINIST and during
479 treatment. Signs and symptoms of heart problems may include:
 - 480 • feeling like your heart is pounding or racing
 - 481 • shortness of breath
 - 482 • swelling of your ankles and feet
 - 483 • feeling lightheaded
- 484 • **eye problems.** MEKINIST can cause eye problems including blindness. Tell your
485 healthcare provider right away if you get these symptoms of eye problems:
 - 486 • blurred vision, loss of vision, or other vision changes
 - 487 • see color dots
 - 488 • halo (seeing blurred outline around objects)
- 489 • **lung or breathing problems.** Tell your healthcare provider if you have any
490 new or worsening symptoms of lung or breathing problems, including:
 - 491 • shortness of breath
 - 492 • cough
- 493 • **skin rash.** Rash is the most common side effect of MEKINIST and in some cases
494 can be severe and can result in admission to the hospital if severe. Tell your
495 healthcare provider if you get any of the following symptoms:
 - 496 • skin rash
 - 497 • acne
 - 498 • redness, swelling, peeling, or tenderness of hands or feet

499 • skin redness

500 **The most common side effects of MEKINIST include:**

501 • diarrhea

502 • swelling of the face, arms, or legs

503 **MEKINIST can cause new or worsening high blood pressure**

504 **(hypertension)**. Your healthcare provider should check your blood pressure during
505 treatment with MEKINIST. Tell your healthcare provider if you develop high blood
506 pressure, your blood pressure worsens, or you have severe headache,
507 lightheadedness, or dizziness.

508

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

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

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

515 **How should I store MEKINIST?**

516 • Store MEKINIST in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not
517 freeze.

518 • Keep MEKINIST dry and away from moisture.

519 • The bottle of MEKINIST contains a desiccant packet to help keep your medicine
520 dry. Do not throw away the desiccant packet.

521 • Keep MEKINIST in its original bottle. Do not place tablets in a pill box.

522 • Safely throw away MEKINIST that is out of date or no longer needed.

523 **Keep MEKINIST and all medicine out of the reach of children.**

524 **General information about MEKINIST**

525 Medicines are sometimes prescribed for purposes other than those listed in a
526 Patient Information Leaflet. Do not use MEKINIST for a condition for which it was
527 not prescribed. Do not give MEKINIST to other people, even if they have the same
528 symptoms that you have. It may harm them.

529 You can ask your healthcare provider or pharmacist for information about
530 MEKINIST that is written for health professionals.

531 For more information, go to www.MEKINIST.com or call 1-888-825-5249.

532 **What are the ingredients in MEKINIST?**

533 **Active ingredient:** trametinib

534 **Inactive ingredients:**

535 Tablet Core: mannitol, microcrystalline cellulose, hypromellose, croscarmellose
536 sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal
537 silicon dioxide. Tablet Coating: hypromellose, titanium dioxide, polyethylene glycol,
538 polysorbate 80 (2-mg tablets), iron oxide yellow (0.5-mg tablets), iron oxide red
539 (2-mg tablets).

540

541 This Patient Information has been approved by the U.S. Food and Drug
542 Administration.

543

544 MEKINIST is a trademark of GlaxoSmithKline.



545

546 GlaxoSmithKline

547 Research Triangle Park, NC 27709

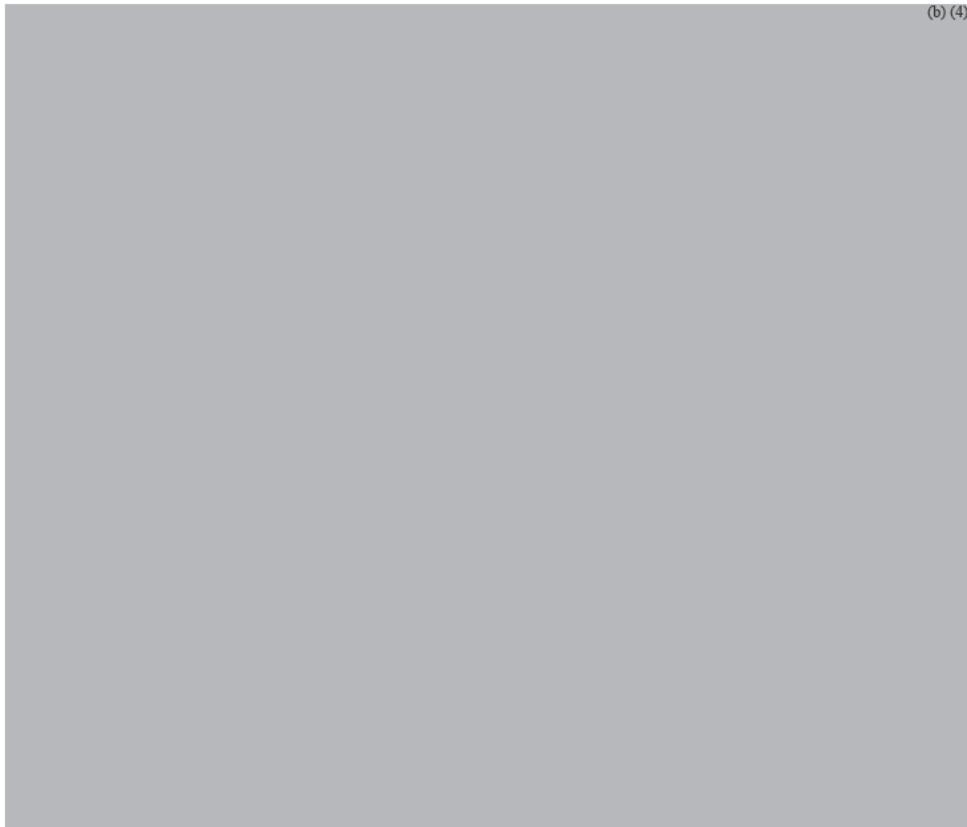
548

549 ©2013, GlaxoSmithKline. All rights reserved.

550

551 Issued: May 2013

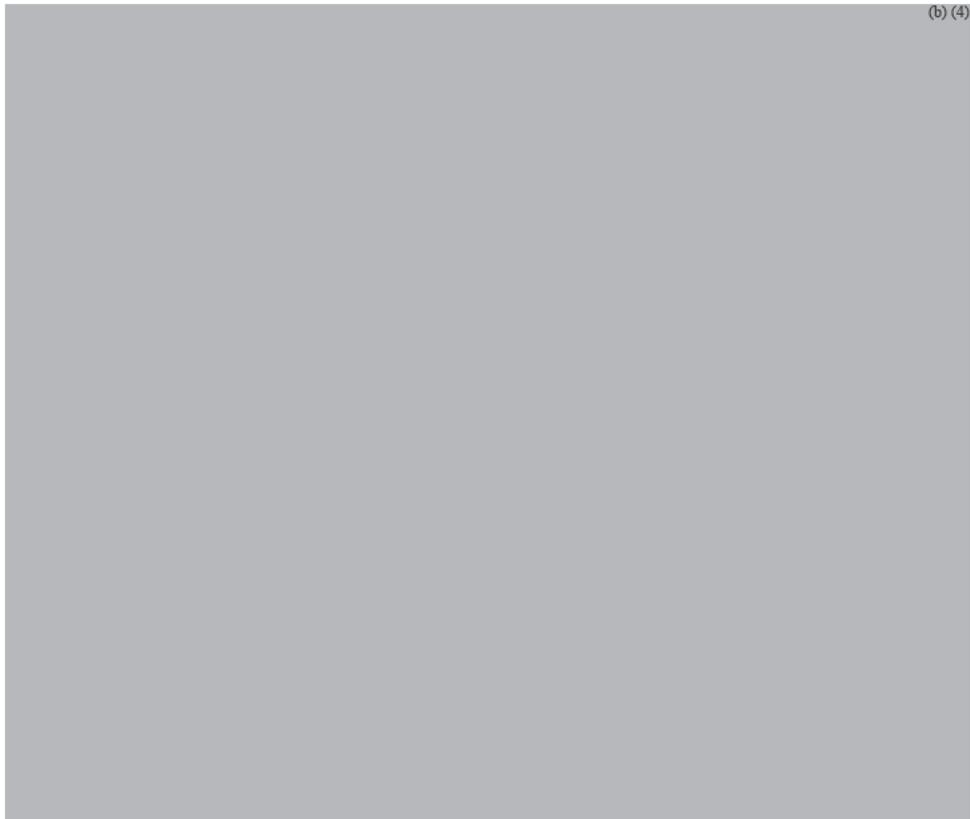
552 MKN: 1PIL



(b) (4)

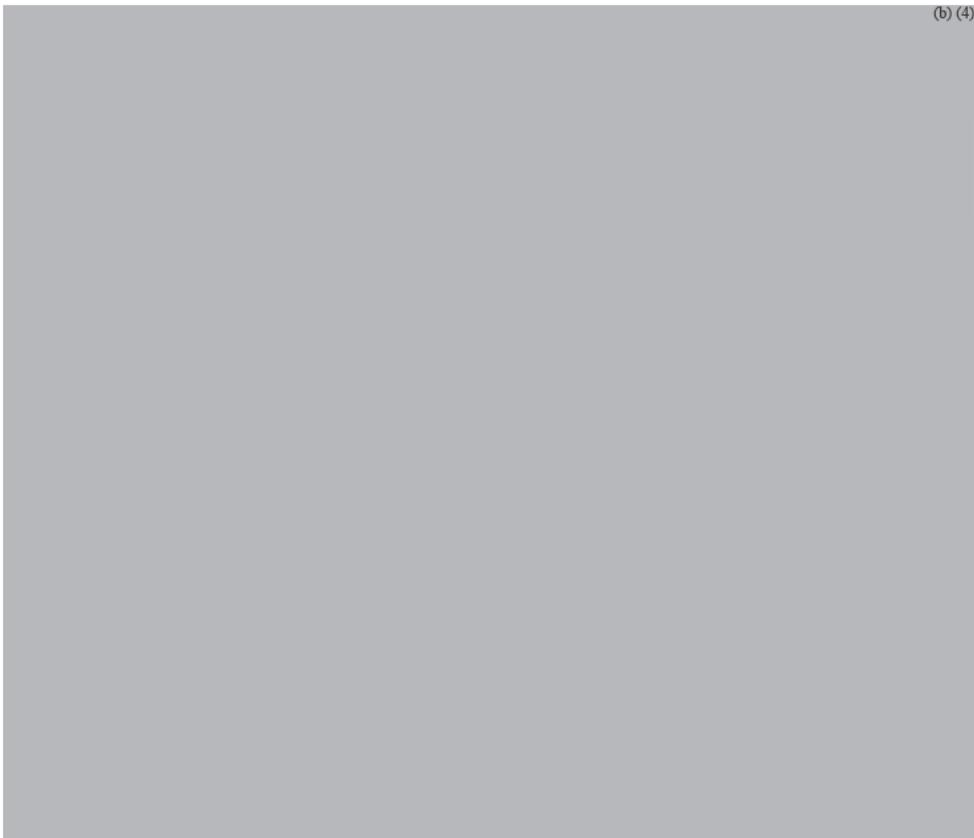
(b) (4)







(b) (4)





(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
05/29/2013