

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

-----RECENT MAJOR CHANGES-----

Indications and Usage (1)	11/2015
Dosage and Administration (2.2, 2.3)	11/2015
Warnings and Precautions (5)	11/2015

-----INDICATIONS AND USAGE-----

MEKINIST is a kinase inhibitor indicated, as a single agent or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1, 14.1)

Limitation of use: MEKINIST is not indicated for 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 dosage regimen of MEKINIST is 2 mg orally once daily. Take MEKINIST at least 1 hour before or at least 2 hours after a meal. (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 0.5 mg and 2 mg. (3)

-----CONTRAINDICATIONS-----

None. (4)

-----WARNINGS AND PRECAUTIONS-----

- New primary malignancies, cutaneous and non-cutaneous:** can occur when MEKINIST is used with dabrafenib. Monitor patients for new malignancies prior to initiation of therapy while on therapy, and following discontinuation of treatment. (5.1, 2.3)
- Hemorrhage:** Major hemorrhagic events can occur. Monitor for signs and symptoms of bleeding (5.2, 2.3)
- Venous thromboembolism:** Deep vein thrombosis and pulmonary embolism can occur in patients receiving MEKINIST. (5.3, 2.3).
- Cardiomyopathy:** Assess LVEF before treatment, after one month of treatment, then every 2 to 3 months thereafter. (5.4, 2.3)
- Ocular toxicities:** Perform ophthalmologic evaluation for any visual disturbances. For Retinal Vein Occlusion (RVO), permanently discontinue MEKINIST. (5.5, 2.3).

- Interstitial lung disease (ILD):** Withhold MEKINIST for new or progressive unexplained pulmonary symptoms. Permanently discontinue MEKINIST for treatment-related ILD or pneumonitis. (5.6, 2.3)
- Serious febrile reactions:** Can occur when MEKINIST is used with dabrafenib. (5.7, 2.3)
- Serious skin toxicity:** Monitor for skin toxicities and for secondary infections. Discontinue MEKINIST for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of MEKINIST. (5.8, 2.3)
- Hyperglycemia:** Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia. (5.9, 2.3)
- Embryo-fetal toxicity:** MEKINIST can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)

-----ADVERSE REACTIONS-----

- Most common adverse reactions ($\geq 20\%$) for MEKINIST as a single agent include rash, diarrhea, and lymphedema. (6.1)
- Most common adverse reactions ($\geq 20\%$) for MEKINIST with dabrafenib include pyrexia, nausea, rash, chills, diarrhea, vomiting, hypertension, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Avoid concurrent administration of strong inhibitors of CYP3A4 or CYP2C8 when MEKINIST is used with dabrafenib. (7.1)
- Avoid concurrent administration of strong inducers of CYP3A4 or CYP2C8 when MEKINIST is used with dabrafenib. (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 when MEKINIST is used with dabrafenib. (7.1)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Do not breast feed. (8.2)
- Females and Males of Reproductive Potential: May impair fertility. Counsel patients on pregnancy planning and prevention. (8.3)

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

Revised: 11/2015

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 MEKINIST[®] is indicated, as a single agent or in combination with dabrafenib, for the treatment
4 of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations,
5 as detected by an FDA-approved test [see *Clinical 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 the presence of BRAF V600E or V600K mutation in tumor specimens [see *Clinical Studies*
12 *(14.1)*]. Information on FDA-approved tests for the detection of BRAF V600 mutations in
13 melanoma is available at: <http://www.fda.gov/CompanionDiagnostics>.

14 **2.2 Recommended Dosing**

15 The recommended dosage regimen is MEKINIST 2 mg orally taken once daily at the same time
16 each day as a single agent or with dabrafenib. Continue treatment until disease progression or
17 unacceptable toxicity occurs.

18 Take MEKINIST at least 1 hour before or 2 hours after a meal [see *Clinical Pharmacology*
19 *(12.3)*]. Do not take a missed dose of MEKINIST within 12 hours of the next dose of
20 MEKINIST.

21 **2.3 Dose Modifications**

22 Review the Full Prescribing Information for dabrafenib for recommended dose modifications.
23 Dose modifications are not recommended for MEKINIST when administered with dabrafenib for
24 the following adverse reactions of dabrafenib: non-cutaneous malignancies and uveitis.

25 **For New Primary Cutaneous Malignancies**

26 No dose modifications are required.
27
28

29 **Table 1. Recommended Dose Reductions**

Dose Reductions for MEKINIST	
First Dose Reduction	1.5 mg orally once daily
Second Dose Reduction	1 mg orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate MEKINIST 1 mg orally once daily

30 **Table 2. Recommended Dose Modifications for MEKINIST**

Severity of Adverse Reaction^a	MEKINIST^b
<i>Febrile Drug Reaction</i>	
<ul style="list-style-type: none"> Fever higher than 104°F Fever complicated by rigors, hypotension, dehydration, or renal failure 	Withhold MEKINIST until fever resolves. Then resume MEKINIST at same or lower dose level.
<i>Cutaneous</i>	
<ul style="list-style-type: none"> Intolerable Grade 2 skin toxicity Grade 3 or 4 skin toxicity 	Withhold MEKINIST for up to 3 weeks. <ul style="list-style-type: none"> If improved, resume at a lower dose level. If not improved, permanently discontinue.
<i>Cardiac</i>	
<ul style="list-style-type: none"> Asymptomatic, absolute decrease in left ventricular ejection fraction (LVEF) of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pretreatment value 	Withhold MEKINIST for up to 4 weeks. <ul style="list-style-type: none"> If improved to normal LVEF value, resume at a lower dose level. If not improved to normal LVEF value, permanently discontinue.
<ul style="list-style-type: none"> Symptomatic congestive heart failure Absolute decrease in LVEF of greater than 20% from baseline that is below LLN 	Permanently discontinue MEKINIST.
<i>Venous Thromboembolism</i>	
<ul style="list-style-type: none"> Uncomplicated DVT or PE 	Withhold MEKINIST for up to 3 weeks. <ul style="list-style-type: none"> If improved to Grade 0-1, resume at a lower dose level. If not improved, permanently discontinue.
<ul style="list-style-type: none"> Life threatening PE 	Permanently discontinue MEKINIST.
<i>Ocular Toxicities</i>	

Severity of Adverse Reaction ^a	MEKINIST ^b
<ul style="list-style-type: none"> • Retinal pigment epithelial detachments (RPED) 	Withhold MEKINIST for up to 3 weeks. <ul style="list-style-type: none"> • If improved, resume MEKINIST at same or lower dose level. • If not improved, discontinue or resume at a lower dose.
<ul style="list-style-type: none"> • Retinal vein occlusion 	Permanently discontinue MEKINIST.
<i>Pulmonary</i>	
<ul style="list-style-type: none"> • Interstitial lung disease/pneumonitis 	Permanently discontinue MEKINIST.
<i>Other</i>	
<ul style="list-style-type: none"> • Intolerable Grade 2 adverse reactions • Any Grade 3 adverse reactions 	Withhold MEKINIST <ul style="list-style-type: none"> • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
<ul style="list-style-type: none"> • First occurrence of any Grade 4 adverse reaction 	<ul style="list-style-type: none"> • Withhold MEKINIST until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or <ul style="list-style-type: none"> • Permanently discontinue.
<ul style="list-style-type: none"> • Recurrent Grade 4 adverse reaction 	Permanently discontinue MEKINIST.

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

33 ^b See Table 1 for recommended dose reductions of MEKINIST.

34 **3 DOSAGE FORMS AND STRENGTHS**

35 0.5 mg tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one
36 face and ‘TFC’ on the opposing face.

37 2 mg tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and
38 ‘HMJ’ on the opposing face.

39 **4 CONTRAINDICATIONS**

40 None.

41 **5 WARNINGS AND PRECAUTIONS**

42 Review the Full Prescribing Information for dabrafenib for information on the serious risks of
43 dabrafenib prior to initiation of MEKINIST with dabrafenib.

44 **5.1 New Primary Malignancies**

45 New primary malignancies, cutaneous and non-cutaneous, can occur when MEKINIST is
46 administered with dabrafenib.

47 Cutaneous Malignancies

48 In Trial 2, the incidence of basal cell carcinoma in patients receiving MEKINIST and dabrafenib
49 was 3.3% (7/209) compared with 6% (13/211) in patients receiving single-agent dabrafenib. The
50 median time to first diagnosis of basal cell carcinoma was 5.1 months (range: 2.8 to 23.9
51 months) in the MEKINIST plus dabrafenib arm and was 4.4 months (range: 29 days to 16.5
52 months) in the dabrafenib arm. Among the 7 patients receiving MEKINIST with dabrafenib who
53 developed basal cell carcinoma, 2 (29%) experienced more than one occurrence (range: 1 to 3).

54 Cutaneous squamous cell carcinomas (cuSCC) and keratoacanthoma occurred in 3% of patients
55 receiving MEKINIST and dabrafenib and 10% of patients receiving single-agent dabrafenib. The
56 median time to first diagnosis of cuSCC was 7.3 months (range: 1.8 to 16.8 months) in the
57 MEKINIST plus dabrafenib arm and was 2 months (range: 9 days to 20.9 months) in the
58 dabrafenib arm.

59 New primary melanoma occurred in 0.5% (1/209) of patients receiving MEKINIST and
60 dabrafenib and in 1.9% (4/211) of patients receiving dabrafenib alone.

61 Perform dermatologic evaluations prior to initiation of MEKINIST when used with dabrafenib,
62 every 2 months while on therapy, and for up to 6 months following discontinuation of the
63 combination. No dose modifications of MEKINIST are recommended in patients who develop
64 new primary cutaneous malignancies.

65 Non-Cutaneous Malignancies

66 Based on its mechanism of action, dabrafenib may promote growth and development of
67 malignancies with activation of RAS through mutation or other mechanisms [*refer to the Full*
68 *Prescribing Information for dabrafenib*]. In Trial 2, non-cutaneous malignancies occurred in
69 1.4% (3/209) of patients receiving MEKINIST plus dabrafenib and in 2.8% (6/211) of patients
70 receiving single-agent dabrafenib.

71 Monitor patients receiving MEKINIST and dabrafenib closely for signs or symptoms of non-
72 cutaneous malignancies. No dose modification is required for MEKINIST in patients who
73 develop non-cutaneous malignancies [*see Dosage and Administration (2.3)*].

74 **5.2 Hemorrhage**

75 Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or
76 organ, can occur with MEKINIST.

77 In Trial 2, the incidence of hemorrhagic events in patients receiving MEKINIST and dabrafenib
78 was 19% (40/209) compared with 15% (32/211) of patients receiving dabrafenib alone.
79 Gastrointestinal hemorrhage occurred in 6% (12/209) of patients receiving MEKINIST in
80 combination with dabrafenib compared with 2.8% (6/211) of patients receiving single-agent
81 dabrafenib. In Trial 2, 1.4% (3/209) of patients receiving MEKINIST and dabrafenib developed
82 fatal intracranial hemorrhage compared with none of the patients receiving single-agent
83 dabrafenib alone.

84 Permanently discontinue MEKINIST for all Grade 4 hemorrhagic events and for any Grade 3
85 hemorrhagic events that do not improve. Withhold MEKINIST for Grade 3 hemorrhagic events;
86 if improved, resume at the next lower dose level.

87 **5.3 Venous Thromboembolism**

88 Venous thromboembolism can occur with MEKINIST.

89 In Trial 2, deep venous thrombosis (DVT) and pulmonary embolism (PE) occurred in 2.8%
90 (6/209) of patients receiving MEKINIST and dabrafenib compared with 0.9% (2/211) of patients
91 receiving single-agent dabrafenib.

92 Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such
93 as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEKINIST
94 for life threatening PE. Withhold MEKINIST for uncomplicated DVT and PE for up to 3 weeks;
95 if improved, MEKINIST may be resumed at a lower dose level [*see Dosage and Administration*
96 (2.3)].

97 **5.4 Cardiomyopathy**

98 Cardiomyopathy, including cardiac failure, can occur with MEKINIST.

99 In clinical trials of MEKINIST, all patients were required to have an echocardiogram at baseline
100 to document normal LVEF and repeat echocardiograms at Week 4, Week 12, and every 12
101 weeks thereafter.

102 In Trial 1, cardiomyopathy [defined as cardiac failure, left ventricular dysfunction, or decreased
103 left ventricular ejection fraction (LVEF)] occurred in 7% (14/211) of patients receiving
104 MEKINIST; no chemotherapy-treated patient in Trial 1 developed cardiomyopathy. The median
105 time to onset of cardiomyopathy in patients receiving MEKINIST was 2.1 months (range: 16
106 days to 5.1 months); cardiomyopathy was identified within the first month of receiving
107 MEKINIST in five of these 14 patients. Four percent of patients in Trial 1 required
108 discontinuation (4/211) and/or dose reduction (7/211) of MEKINIST. Cardiomyopathy resolved
109 in 10 of these 14 (71%) patients.

110 Across clinical trials of MEKINIST as a single agent (N = 329), 11% of patients developed
111 evidence of cardiomyopathy [decrease in LVEF below institutional lower limits of normal (LLN)
112 with an absolute decrease in LVEF $\geq 10\%$ below baseline] and 5% demonstrated a decrease in LVEF
113 below institutional LLN with an absolute decrease in LVEF of $\geq 20\%$ below baseline.

114 In Trial 2, evidence of cardiomyopathy (decrease in LVEF below the institutional LLN with an
115 absolute decrease in LVEF $\geq 10\%$ below baseline) occurred in 6% (12/206) of patients receiving
116 MEKINIST and dabrafenib and in 2.9% (6/207) of patients receiving single-agent dabrafenib.
117 The median time to onset of cardiomyopathy in patients receiving MEKINIST and dabrafenib
118 was 8.2 months (range: 28 days to 24.9 months); cardiomyopathy was identified within the first
119 month of receiving MEKINIST and dabrafenib in 2 of these 12 patients. In patients receiving
120 MEKINIST and dabrafenib, cardiomyopathy resulted in dose interruption (4.4%), dose reduction
121 (2.4%), and permanent discontinuation (1.5%) of MEKINIST. Cardiomyopathy resolved in 10 of
122 12 patients receiving MEKINIST and dabrafenib.

123 Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of
124 MEKINIST as a single agent or with dabrafenib, one month after initiation, and then at 2- to 3-
125 month intervals while on treatment. Withhold MEKINIST for up to 4 weeks if absolute LVEF
126 value decreases by 10% from pretreatment values and is less than the lower limit of normal. For
127 symptomatic cardiomyopathy or persistent, asymptomatic LV dysfunction of $>20\%$ from
128 baseline that is below LLN that does not resolve within 4 weeks, permanently discontinue
129 MEKINIST [*see Dosage and Administration (2.3)*].

130 **5.5 Ocular Toxicities**

131 Retinal Vein Occlusion (RVO)

132 Across all clinical trials with MEKINIST, the incidence of RVO was 0.2% (4/1,749). RVO may
133 lead to macular edema, decreased visual function, neovascularization, and glaucoma.

134 Urgently (within 24 hours) perform ophthalmological evaluation for patient-reported loss of
135 vision or other visual disturbances. Permanently discontinue MEKINIST in patients with
136 documented RVO [*see Dosage and Administration (2.3)*].

137 Retinal Pigment Epithelial Detachment (RPED)

138 Retinal pigment epithelial detachment (RPED) can occur with MEKINIST administration.
139 Retinal detachments may be bilateral and multifocal, occurring in the central macular region of
140 the retina or elsewhere in the retina. In Trial 1 and Trial 2, routine monitoring of patients to
141 detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is
142 unknown.

143 Perform ophthalmological evaluation periodically and at any time a patient reports visual
144 disturbances. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is
145 documented on repeat ophthalmological evaluation within 3 weeks, resume MEKINIST. Reduce

146 the dose or discontinue MEKINIST if no improvement after 3 weeks [*see Dosage and*
147 *Administration (2.3)*].

148 **5.6 Interstitial Lung Disease**

149 In clinical trials of single-agent MEKINIST (N = 329), ILD or pneumonitis occurred in 2% of
150 patients. In Trial 1, 2.4% (5/211) of patients treated with MEKINIST developed ILD or
151 pneumonitis; all five patients required hospitalization. The median time to first presentation of
152 ILD or pneumonitis was 5.3 months (range: 2 to 5.7 months). In Trial 2, 1.0% (2/209) of patients
153 receiving MEKINIST and dabrafenib developed pneumonitis compared with none of the patients
154 receiving single-agent dabrafenib.

155 Withhold MEKINIST in patients presenting with new or progressive pulmonary symptoms and
156 findings including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical
157 investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-
158 related ILD or pneumonitis [*see Dosage and Administration (2.3)*].

159 **5.7 Serious Febrile Reactions**

160 Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills,
161 dehydration, or renal failure, can occur when MEKINIST is administered with dabrafenib.

162 Fever (serious and non-serious) occurred in 57% (119/209) of patients receiving MEKINIST and
163 dabrafenib and in 33% (69/211) of patients receiving dabrafenib alone. The median time to
164 initial onset of fever was 1.2 months (range: 1 day to 23.5 months) with a median duration of
165 fever of 3 days (range: 1 day to 1.7 months) on the MEKINIST plus dabrafenib arm compared
166 with a median time to initial onset of fever of 20 days (range: 1 day to 22.9 months) and median
167 duration of fever of 3 days (range: 1 day to 1.9 months) on the dabrafenib arm. Approximately
168 one-half of the patients who received MEKINIST and dabrafenib and experienced pyrexia had
169 three or more discrete episodes.

170 Across clinical trials of MEKINIST administered with dabrafenib, serious febrile reactions or
171 fever of any severity complicated by severe rigors/chills hypotension, dehydration, renal failure,
172 or syncope, occurred in 17% (93/559) of patients receiving MEKINIST and dabrafenib. Fever
173 was complicated by severe chills/rigors in 0.4% (2/559), dehydration in 1.8% (10/559), renal
174 failure in 0.5% (3/559), and syncope in 0.7% (4/559) of patients.

175 Withhold MEKINIST for fever higher than 104°F or for serious febrile reactions or fever
176 accompanied by hypotension, rigors or chills, dehydration, or renal failure, and evaluate for signs
177 and symptoms of infection. Monitor serum creatinine and other evidence of renal function during
178 and following severe pyrexia. Refer to Table 2 for recommended dose modifications for adverse
179 reactions [*see Dosage and Administration (2.3)*]. Administer antipyretics as secondary
180 prophylaxis when resuming MEKINIST if patient had a prior episode of severe febrile reaction
181 or fever associated with complications. Administer corticosteroids (e.g., prednisone 10 mg daily)
182 for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline

183 within 3 days of onset of pyrexia, or for pyrexia associated with complications such as
184 dehydration, hypotension renal failure, or severe chills/rigors, and there is no evidence of active
185 infection.

186 **5.8 Serious Skin Toxicity**

187 Serious skin toxicity can occur with MEKINIST.

188 In Trial 1, the overall incidence of any skin toxicity, the most common of which were rash,
189 dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema, was 87%
190 in patients receiving MEKINIST and 13% in chemotherapy-treated patients. Severe skin toxicity
191 occurred in 12% of patients treated with MEKINIST. Skin toxicity requiring hospitalization
192 occurred in 6% of patients treated with MEKINIST, most commonly for secondary infections of
193 the skin requiring intravenous antibiotics or severe skin toxicity without secondary infection. In
194 comparison, no patients treated with chemotherapy required hospitalization for severe skin
195 toxicity or infections of the skin. The median time to initial onset of skin toxicity in patients
196 treated with MEKINIST was 15 days (range: 1 day to 7.3 months) and median time to resolution
197 of skin toxicity was 1.6 months (range: 1 day to 9.3 months). Reductions in the dose of
198 MEKINIST were required in 12% and permanent discontinuation of MEKINIST was required in
199 1% of patients with skin toxicity.

200 In Trial 2, the overall incidence of any skin toxicity was 55% for patients receiving MEKINIST
201 and dabrafenib compared with 55% for patients receiving single-agent dabrafenib. No serious or
202 severe cases of skin toxicity occurred in patients treated with MEKINIST and dabrafenib. The
203 median time to initial onset of skin toxicity for patients receiving MEKINIST with dabrafenib
204 was 1.9 months (range: 1 day to 22.1 months) and median time to resolution of skin toxicity for
205 patients receiving MEKINIST with dabrafenib was 1.2 months (range: 1 day to 24.4 months).
206 Reductions in the dose of MEKINIST were required in 5% of patients receiving MEKINIST and
207 dabrafenib and no patients required permanent discontinuation of MEKINIST for skin toxicity.

208 Across clinical trials of MEKINIST administered with dabrafenib (N = 559), serious skin
209 toxicity occurred in 0.7% (4/559) of patients.

210 Withhold MEKINIST for intolerable or severe skin toxicity. Resume MEKINIST at reduced
211 doses in patients with improvement or recovery from skin toxicity within 3 weeks [*see Dosage*
212 *and Administration (2.3)*].

213 **5.9 Hyperglycemia**

214 Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycemic
215 agent therapy can occur when MEKINIST is administered with dabrafenib.

216 In Trial 2, 27% (4/15) of patients with a history of diabetes who received MEKINIST and
217 dabrafenib and 13% (2/16) of patients with a history of diabetes who received single-agent
218 dabrafenib required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia

219 based on laboratory values occurred in 5% (11/208) and 0.5% (1/208) of patients receiving
220 MEKINIST and dabrafenib, respectively, compared with 4.3% (9/209) for Grade 3
221 hyperglycemia and no patients with Grade 4 hyperglycemia for patients receiving single-agent
222 dabrafenib.

223 Monitor serum glucose levels upon initiation and as clinically appropriate when MEKINIST is
224 administered with dabrafenib in patients with pre-existing diabetes or hyperglycemia.

225 **5.10 Embryo-Fetal Toxicity**

226 Based on findings from animal studies and its mechanism of action, MEKINIST can cause fetal
227 harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in
228 rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the
229 human exposure at the recommended clinical dose. If MEKINIST is used during pregnancy, or if
230 the patient becomes pregnant while taking MEKINIST, advise the patient of the potential risk to
231 a fetus [see *Use in Specific Populations (8.1)*].

232 Advise female patients of reproductive potential to use effective contraception during treatment
233 with MEKINIST and for 4 months after treatment. Advise patients to contact their healthcare
234 provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST [see
235 *Use in Specific Populations (8.1, 8.3)*].

236 **6 ADVERSE REACTIONS**

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

- 238 • New Primary Malignancies [see *Warnings and Precautions (5.1)*]
- 239 • Hemorrhage [see *Warnings and Precautions (5.2)*]
- 240 • Venous Thromboembolism [see *Warnings and Precautions (5.3)*]
- 241 • Cardiomyopathy [see *Warnings and Precautions (5.4)*]
- 242 • Ocular Toxicities [see *Warnings and Precautions (5.5)*]
- 243 • Interstitial Lung Disease [see *Warnings and Precautions (5.6)*]
- 244 • Serious Febrile Reactions [see *Warnings and Precautions (5.7)*]
- 245 • Serious Skin Toxicity [see *Warnings and Precautions (5.8)*]
- 246 • Hyperglycemia [see *Warnings and Precautions (5.9)*]

247 **6.1 Clinical Trials Experience**

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

251 The data described in the Warnings and Precautions section and below reflect exposure to
252 MEKINIST as a single agent and in combination with dabrafenib.

253 MEKINIST Administered as a Single Agent

254 MEKINIST as a single agent was evaluated in 329 patients including 107 (33%) exposed for
255 greater than or equal to 6 months and 30 (9%) exposed for greater than or equal to one year.
256 MEKINIST as a single agent was studied in open-label, single-arm trials (N = 118) or in an
257 open-label, randomized, active-controlled trial (N = 211). The median age was 54 years, 60%
258 were male, >99% were White, and all patients had metastatic melanoma. All patients received
259 2 mg once-daily doses of MEKINIST.

260 Table 3 presents adverse reactions identified from analyses of Trial 1, a randomized, open-label
261 trial of patients with BRAF V600E or V600K mutation-positive melanoma receiving
262 MEKINIST (N = 211) 2 mg orally once daily or chemotherapy (N = 99) (either dacarbazine
263 1,000 mg/m² every 3 weeks or paclitaxel 175 mg/m² every 3 weeks) [*see Clinical Studies*
264 *(14.1)*]. Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or
265 current evidence of Class II or greater congestive heart failure (New York Heart Association)
266 were excluded from Trial 1. The median duration of treatment with MEKINIST was 4.3 months.
267 In Trial 1, 9% of patients receiving MEKINIST experienced adverse reactions resulting in
268 permanent discontinuation of trial medication. The most common adverse reactions resulting in
269 permanent discontinuation of MEKINIST were decreased left ventricular ejection fraction
270 (LVEF), pneumonitis, renal failure, diarrhea, and rash. Adverse reactions led to dose reductions
271 in 27% of patients treated with MEKINIST. Rash and decreased LVEF were the most common
272 reasons cited for dose reductions of MEKINIST.

273

274 **Table 3. Selected Adverse Reactions Occurring in ≥10% of Patients Receiving MEKINIST**
 275 **and at a Higher Incidence (≥5%) than in the Chemotherapy Arm or ≥2% (Grades 3 or 4)**
 276 **Adverse Reactions**

Adverse Reactions	MEKINIST N = 211		Chemotherapy N = 99	
	All Grades ^a	Grades 3 and 4 ^b	All Grades ^a	Grades 3 and 4 ^b
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Acneiform dermatitis	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 ^c	15	2	2	0
Abdominal pain ^d	13	1	5	1
Vascular disorders				
Lymphedema ^e	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage ^f	13	<1	0	0

277 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
 278 ^b Grade 4 adverse reactions limited to rash (n = 1) in trametinib arm and diarrhea (n = 1) in chemotherapy arm.
 279 ^c Includes stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.
 280 ^d Includes abdominal pain, lower abdominal pain, upper abdominal pain, and abdominal tenderness.
 281 ^e Includes lymphedema, edema, and peripheral edema.
 282 ^f Includes epistaxis, gingival bleeding, hemochezia, rectal hemorrhage, melena, vaginal hemorrhage,
 283 hemorrhoidal hemorrhage, hematuria, and conjunctival hemorrhage.
 284

285 Other clinically important adverse reactions observed in less than or equal to 10% of patients
 286 (N = 329) treated with MEKINIST were:

287 *Cardiac Disorders:* Bradycardia

288 *Gastrointestinal Disorders:* Dry mouth.

289 *Infections and Infestations:* Folliculitis, rash pustular, cellulitis.

290 *Musculoskeletal and Connective Tissue Disorders:* Rhabdomyolysis.

291 *Nervous System Disorders:* Dizziness, dysgeusia.

292 *Ocular Disorders:* Blurred vision, dry eye.

293

294 **Table 4. Percent-Patient Incidence of Laboratory Abnormalities Occurring at a Higher**
295 **Incidence in Patients Treated with MEKINIST in Trial 1 [Between-arm Difference of $\geq 5\%$**
296 **(All Grades) or $\geq 2\%$ (Grades 3 or 4)^a**

Test	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
Hypoalbuminemia	42	2	23	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

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

298

299 **MEKINIST Administered with Dabrafenib**

300 The safety of MEKINIST, administered with dabrafenib, was evaluated in 559 patients with
301 previously untreated, unresectable or metastatic, BRAF V600 mutation-positive melanoma who
302 received Mekinist in two trials, Trial 2 (n = 209) multicenter, double-blind, randomized (1:1),
303 active-controlled trial and Trial 3 (n = 350) a multicenter, open-label, randomized (1:1), active-
304 controlled trial. In both trials, patients received MEKINIST 2 mg orally once daily and
305 dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity. The
306 trials excluded patients with abnormal left ventricular ejection fraction, history of acute coronary
307 syndrome within 6 months, history of Class II or greater congestive heart failure (New York
308 Heart Association), history of RVO or RPED, QTcB interval ≥ 480 msec, uncontrolled
309 hypertension, uncontrolled arrhythmias, active brain metastases, or known history of G6PD
310 deficiency.

311 Among these 559 patients, 197 (35%) were exposed to MEKINIST for >6 months to 12 months
312 while 185 (33%) were exposed to MEKINIST for >1 year. The median age was 55 years (range:
313 18 to 91), 57% were male, and 98% were White, 72% had baseline ECOG performance status 0
314 and 28% had ECOG performance status 1, 64% had M1c stage disease, 35% had elevated LDH
315 at baseline, and 0.5% had a history of brain metastases.

316 The most commonly occurring adverse reactions ($\geq 20\%$) for MEKINIST in patients receiving
317 MEKINIST plus dabrafenib were: pyrexia, nausea, rash, chills, diarrhea, vomiting, hypertension,
318 and peripheral edema.

319 The demographics and baseline tumor characteristics of patients enrolled in Trial 2 are
320 summarized in Clinical Studies [see *Clinical Studies (14.1)*]. Patients receiving MEKINIST plus
321 dabrafenib had a median duration of exposure of 11 months (range: 3 days to 30 months) to

322 MEKINIST. Among the 209 patients receiving MEKINIST plus dabrafenib, 26% were exposed
323 to MEKINIST for >6 months to 12 months while 46% were exposed to MEKINIST for >1 year.

324 In Trial 2, adverse reactions leading to discontinuation of MEKINIST occurred in 11% of
325 patients receiving MEKINIST plus dabrafenib; the most common were pyrexia (1.4%) and
326 decreased ejection fraction (1.4%). Adverse reactions leading to dose reductions of MEKINIST
327 occurred in 18% of patients receiving MEKINIST plus dabrafenib; the most common were
328 pyrexia (2.9%), neutropenia (1.9%), decreased ejection fraction (1.9%), and rash (1.9%).

329 Adverse reactions leading to dose interruptions of MEKINIST occurred in 46% of patients
330 receiving MEKINIST plus dabrafenib; the most common were pyrexia (18%), chills (7%),
331 vomiting (6%) and decreased ejection fraction (4.8%).

332 Table 5 and Table 6 present selected adverse drug reactions and laboratory abnormalities,
333 respectively, of MEKINIST observed in Trial 2.

334

335 **Table 5. Incidence of Adverse Reactions Occurring in $\geq 10\%$ (All Grades) of Patients**
 336 **Receiving MEKINIST with Dabrafenib and at a Higher Incidence* than in Patients**
 337 **Receiving Single-Agent Dabrafenib in Trial 2^a**

Adverse Reactions	Pooled MEKINIST plus Dabrafenib N = 559		Trial 2			
	All Grades (%)	Grades 3 and 4 (%)	MEKINIST plus Dabrafenib N = 209		Dabrafenib N = 211	
			All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General disorders and administrative site conditions						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Edema peripheral ^b	21	0.7	25	1.4	11	0.5
Gastrointestinal disorders						
Nausea	35	0.4	34	0.5	27	1.4
Diarrhea	31	1.3	30	1.4	16	0.9
Vomiting	27	1.1	25	1.0	14	0.5
Abdominal pain ^c	18	0.9	26	1.0	14	2.4
Nervous system disorders						
Dizziness	11	0.2	14	0	7	0
Vascular disorders						
Hypertension	26	11	25	6	16	6
Hemorrhage ^d	18	2.0	19	1.9	15	1.9
Skin and subcutaneous tissue disorders						
Rash ^e	32	1.1	42	0	27	1.4

338 * $\geq 5\%$ for All Grades or $\geq 2\%$ for Grades 3–4 incidence in patients receiving MEKINIST with dabrafenib compared
 339 with patients receiving dabrafenib as a single agent

340 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

341 ^b Includes peripheral edema, edema, lymphedema, localized edema, and generalized edema.

342 ^c Includes abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal discomfort.

343 ^d Most common events ($\geq 1\%$) include epistaxis, hematochezia, decreased hemoglobin, purpura, and rectal
 344 hemorrhage. Grade 4 events were limited to hepatic hematoma and duodenal ulcer hemorrhage (each n = 1 in the
 345 pooled combination arm).

346 ^e Includes rash, generalized rash, pruritic rash, erythematous rash, papular rash, vesicular rash, macular rash,
 347 maculo-papular, and folliculitis rash.

348

349 Other clinically important adverse reactions for MEKINIST observed in less than 10% of
 350 patients receiving MEKINIST in combination with dabrafenib (N = 559) were:

351 *Cardiac Disorders:* bradycardia

352 *Musculoskeletal Disorders*: rhabdomyolysis

353

354 **Table 6. Treatment-Emergent Laboratory Abnormalities Occurring at $\geq 10\%$ (All Grades)**
355 **of Patients Receiving MEKINIST with Dabrafenib and at a Higher Incidence* than in**
356 **Patients Receiving Single-Agent Dabrafenib in Trial 2**

Test	Pooled MEKINIST plus Dabrafenib N = 559 ^a		Trial 2			
			MEKINIST plus Dabrafenib N = 209 ^b		Dabrafenib N = 211 ^b	
	All Grades (%)	Grades 3 and 4 ^c (%)	All Grades (%)	Grades 3 and 4 ^c (%)	All Grades (%)	Grades 3 and 4 ^c (%)
Hematology						
Neutropenia	46	7	50	6	16	1.9
Anemia	43	2.3	43	2.4	38	4.3
Lymphopenia	32	8	38	9	28	7
Thrombocytopenia	21	0.7	19	0.5	10	0.5
Liver Function Tests						
Increased AST	59	4.1	60	4.3	21	1.0
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5
Increased ALT	48	4.5	44	3.8	28	1.0
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypoalbuminemia	48	1.1	53	1.4	27	0
Hyponatremia	25	8	24	6	14	2.9

357 * $\geq 5\%$ for All Grades or $\geq 2\%$ for Grades 3–4 incidence in patients receiving MEKINIST with dabrafenib compared
358 with patients receiving dabrafenib as a single agent

359 AST = Aspartate aminotransferase; ALT = Alanine aminotransferase.

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

361 ^b For these laboratory tests the denominator is 208 for the combination arm, 207-209 for the dabrafenib arm.

362 ^c Grade 4 adverse reactions limited to lymphopenia and hyperglycemia (each n = 4), increased ALT and increased
363 AST (each n = 3), neutropenia (n = 2), and hyponatremia (n = 1), in the pooled combination arm; neutropenia,
364 lymphopenia, increased ALT, increased AST, hyperglycemia (each n = 1) in the Trial 2 combination arm;
365 neutropenia, thrombocytopenia, increased ALT, and increased AST (each n = 1) in the dabrafenib arm.

366 **7 DRUG INTERACTIONS**

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

369 **8 USE IN SPECIFIC POPULATIONS**

370 **8.1 Pregnancy**

371 Risk Summary

372 Based on its mechanism of action and findings from animal reproduction studies, MEKINIST
373 can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology*
374 (12.1)]. There is insufficient data in pregnant women exposed to MEKINIST to assess the risks.
375 Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those
376 resulting in exposures approximately 0.3 times the human exposure at the recommended clinical
377 dose [see *Data*]. If MEKINIST is used during pregnancy, or if the patient becomes pregnant
378 while taking MEKINIST, advise the patient of the potential risk to the fetus.

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

381 Data

382 *Animal Data:* In reproductive toxicity studies, administration of trametinib to rats during the
383 period of organogenesis resulted in decreased fetal weights at doses greater than or equal to
384 0.031 mg/kg/day (approximately 0.3 times the human exposure based on AUC at the
385 recommended dose). In rats, at a dose resulting in exposures 1.8-fold higher than the human
386 exposure at the recommended dose, there was maternal toxicity and an increase in post-
387 implantation loss.

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

395 **8.2 Lactation**

396 Risk Summary

397 There are no data on the presence of trametinib in human milk, or the effects of trametinib on the
398 breastfed infant, or on milk production. Because of the potential for serious adverse reactions in
399 breastfed infants from MEKINIST, advise women not to breastfeed during treatment with
400 MEKINIST and for 4 months following the last dose.

401 **8.3 Females and Males of Reproductive Potential**

402 Based on its mechanism of action and findings from animal reproduction studies, MEKINIST
403 can cause fetal harm when administered to pregnant women [*see Use in Specific Populations*
404 (8.1)].

405 Contraception

406 *Females:* Advise female patients of reproductive potential to use effective contraception during
407 treatment with MEKINIST and for 4 months after the last dose. Advise patients to contact their
408 healthcare provider if they become pregnant, or if pregnancy is suspected, while taking
409 MEKINIST.

410 Infertility

411 *Females:* Advise female patients of reproductive potential that MEKINIST may impair fertility.
412 Increased follicular cysts and decreased corpora lutea were observed in female rats at dose
413 exposures equivalent to 0.3 times the human exposure at the recommended dose [*see Nonclinical*
414 *Toxicology (13.1)*].

415 **8.4 Pediatric Use**

416 The safety and effectiveness of MEKINIST as a single agent or in combination with dabrafenib
417 have not been established in pediatric patients.

418 *Juvenile Animal Data*

419 In a repeat-dose toxicity study in juvenile rats, decreased bone length and corneal dystrophy
420 were observed at doses resulting in exposures as low as 0.3 times the human exposure at the
421 recommended adult dose based on AUC. Additionally, a delay in sexual maturation was noted at
422 doses resulting in exposures as low as 1.6 times the human exposure at the recommended adult
423 dose based on AUC.

424 **8.5 Geriatric Use**

425 Clinical trials of MEKINIST as a single agent did not include sufficient numbers of subjects
426 aged 65 and older to determine whether they respond differently from younger subjects.

427 Of the 559 patients randomized to receive MEKINIST plus dabrafenib in clinical trials, 24%
428 were aged 65 years and older and 6% patients aged 75 years and older. No overall differences in
429 the effectiveness of MEKINIST plus dabrafenib were observed in elderly patients as compared
430 to younger patients. The incidences of peripheral edema (26% vs. 12%) and anorexia (21% vs.
431 9%) increased in elderly patients as compared to younger patients.

432 **8.6 Hepatic Impairment**

433 No dedicated clinical trial has been conducted to evaluate the effect of hepatic impairment on the
434 pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild

435 hepatic impairment based on a population pharmacokinetic analysis [see *Clinical Pharmacology*
436 (12.3)].

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

439 **8.7 Renal Impairment**

440 No formal clinical trial has been conducted to evaluate the effect of renal impairment on the
441 pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild or
442 moderate renal impairment based on a population pharmacokinetic analysis [see *Clinical*
443 *Pharmacology* (12.3)]. The appropriate dose of MEKINIST has not been established in patients
444 with severe renal impairment.

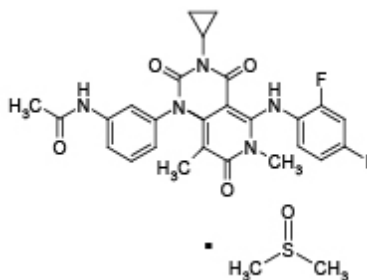
445 **10 OVERDOSAGE**

446 The highest doses of MEKINIST evaluated in clinical trials were 4 mg orally once daily and
447 10 mg administered orally once daily on 2 consecutive days followed by 3 mg once daily. In
448 seven patients treated on one of these two schedules, there were two cases of retinal pigment
449 epithelial detachments for an incidence of 28%.

450 Since trametinib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in
451 the treatment of overdose with MEKINIST.

452 **11 DESCRIPTION**

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



458

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

461 MEKINIST (trametinib) tablets are supplied as 0.5 mg and 2 mg tablets for oral administration.

462 Each 0.5 mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent to 0.5 mg of

463 trametinib non-solvated parent. Each 2 mg tablet contains 2.254 mg trametinib dimethyl
464 sulfoxide equivalent to 2 mg of trametinib non-solvated parent.

465 The inactive ingredients of MEKINIST tablets are: **Tablet Core:** colloidal silicon dioxide,
466 croscarmellose sodium, hypromellose, magnesium stearate (vegetable source), mannitol,
467 microcrystalline cellulose, sodium lauryl sulfate. **Coating:** hypromellose, iron oxide red (2 mg
468 tablets), iron oxide yellow (0.5 mg tablets), polyethylene glycol, polysorbate 80 (2 mg tablets),
469 titanium dioxide.

470 **12 CLINICAL PHARMACOLOGY**

471 **12.1 Mechanism of Action**

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

478 Trametinib and dabrafenib target two different kinases in the RAS/RAF/MEK/ERK pathway.
479 Use of trametinib and dabrafenib in combination resulted in greater growth inhibition of BRAF
480 V600 mutation-positive melanoma cell lines in vitro and prolonged inhibition of tumor growth in
481 BRAF V600 mutation positive melanoma xenografts compared with either drug alone.

482 **12.2 Pharmacodynamics**

483 Administration of 1 mg and 2 mg MEKINIST to patients with BRAF V600 mutation-positive
484 melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of
485 phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a
486 marker of apoptosis).

487 Cardiac Electrophysiology

488 The heart rate-corrected QT (QTc) prolongation potential of trametinib was assessed in a
489 dedicated study in 32 patients who received placebo on day 1 and MEKINIST 2 mg once daily
490 on days 2-14 followed by MEKINIST 3 mg on day 15. No clinically relevant QTc prolongation
491 was detected in the study.

492 In clinical trials in patients receiving MEKINIST plus dabrafenib, QTc prolongation >500 ms
493 occurred in 0.8% (2/264) of patients, and QTc increased by >60 ms from baseline in 3.8%
494 (10/264) of patients.

495 **12.3 Pharmacokinetics**

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

499 Absorption

500 After oral administration of MEKINIST, the median time to achieve peak plasma concentrations
501 (T_{max}) is 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg oral dose of
502 MEKINIST is 72%. The increase in C_{max} was dose proportional after a single dose of 0.125 to 10
503 mg while the increase in AUC was greater than dose proportional. After repeat doses of 0.125 to
504 4 mg daily, both C_{max} and AUC increase proportionally with dose. Inter-subject variability in
505 AUC and C_{max} at steady state is 22% and 28%, respectively.

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

509 Distribution

510 Trametinib is 97.4% bound to human plasma proteins. The apparent volume of distribution
511 (V_d/F) is 214 L.

512 Metabolism

513 Trametinib is metabolized predominantly via deacetylation alone or with mono-oxygenation or
514 in combination with glucuronidation biotransformation pathways in vitro. Deacetylation is
515 mediated by carboxylesterases (i.e., carboxylesterase 1b/c and 2) and may also be mediated by
516 other hydrolytic enzymes.

517 Following a single dose of [^{14}C]-trametinib, approximately 50% of circulating radioactivity is
518 represented as the parent compound. However, based on metabolite profiling after repeat dosing
519 of trametinib, $\geq 75\%$ of drug-related material in plasma is the parent compound.

520 Elimination

521 The estimated elimination half-life of trametinib based on the population PK model is 3.9 to 4.8
522 days. The apparent clearance is 4.9 L/h.

523 Following oral administration of [^{14}C]-trametinib, greater than 80% of excreted radioactivity was
524 recovered in the feces while less than 20% of excreted radioactivity was recovered in the urine
525 with less than 0.1% of the excreted dose as parent.

526 Specific Populations

527 *Age, Body Weight, and Gender:* Based on a population pharmacokinetic analysis, age, sex, and
528 body weight do not have a clinically important effect on the exposure of trametinib. There are

529 insufficient data to evaluate potential differences in the exposure of trametinib by race or
530 ethnicity.

531 *Hepatic Impairment:* Based on a population pharmacokinetic analysis in 64 patients with mild
532 hepatic impairment (total bilirubin \leq ULN and AST $>$ ULN or total bilirubin greater than 1.0 to
533 1.5 x ULN and any AST), mild hepatic impairment has no clinically important effect on the
534 systemic exposure of trametinib. The pharmacokinetics of trametinib have not been studied in
535 patients with moderate or severe hepatic impairment [see *Use in Specific Populations (8.6)*].

536 *Renal Impairment:* As renal excretion of trametinib is low (less than 20%), renal impairment is
537 unlikely to have a clinically important effect on the exposure of trametinib. Based on a
538 population PK analysis in 223 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73
539 m²) and 35 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m²), mild and
540 moderate renal impairment have no clinically important effects on the systemic exposure of
541 trametinib. The pharmacokinetics of trametinib have not been studied in patients with severe
542 renal impairment [see *Use in Specific Populations (8.7)*].

543 *Pediatrics:* No trials have been conducted to evaluate the pharmacokinetics of trametinib in
544 pediatric patients.

545 Drug Interactions

546 *Effect of CYP Enzymes on Trametinib:* Trametinib is not a substrate of CYP enzymes in vitro.

547 *Effect of Trametinib on CYP Substrates:* Based on in vitro studies, trametinib is an inhibitor of
548 CYP2C8, but is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19,
549 CYP2D6, or CYP3A4 at a clinically relevant systemic concentration of 0.04 μ M. Trametinib is
550 an inducer of CYP3A in vitro. Based on cross-study comparisons, oral administration of
551 MEKINIST 2 mg once daily with a sensitive CYP3A4 substrate had no clinically important
552 effect on the AUC and C_{max} of the sensitive CYP3A4 substrate.

553 *Effect of Transporters on Trametinib:* Trametinib is a substrate of P-glycoprotein (P-gp) and bile
554 salt extrusion pump (BSEP). Inhibition of P-gp is unlikely to result in a clinically important
555 increase in trametinib concentrations as trametinib exhibits high passive permeability and
556 bioavailability. Trametinib is not a substrate of breast cancer resistance protein (BCRP), organic
557 anion transporting polypeptide (OATP1B1, OATP1B3, OATP2B1), organic cation transporter 1
558 (OCT1), multidrug resistance protein 2 (MRP2), or multidrug and toxin extrusion 1 (MATE1) in
559 vitro.

560 *Effect of Trametinib on Transporters:* Based on in vitro studies, trametinib is not an inhibitor of
561 P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT1, OAT3), OCT2, BSEP,
562 MRP2, or MATE1 at a clinically relevant systemic concentration of 0.04 μ M.

563 *Effect of Dabrafenib on Trametinib:* Coadministration of trametinib 2 mg daily with dabrafenib
564 150 mg twice daily resulted in no change in AUC of trametinib as compared with administration
565 of trametinib.

566 **13 NONCLINICAL TOXICOLOGY**

567 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

571 Trametinib may impair fertility in humans. In female rats given trametinib for up to 13 weeks,
572 increased follicular cysts and decreased corpora lutea were observed at doses ≥ 0.016 mg/kg/day
573 (approximately 0.3 times the human exposure at the recommended dose based on AUC). In rat
574 and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed on
575 male reproductive tissues. [see *Use in Specific Populations (8.3)*].

576 **14 CLINICAL STUDIES**

577 **14.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic**
578 **Melanoma**

579 Mekinist as a Single Agent

580 The safety and efficacy of MEKINIST were evaluated in an international, multicenter,
581 randomized (2:1), open-label, active-controlled trial (Trial 1) in 322 patients with BRAF V600E
582 or V600K mutation-positive, unresectable or metastatic melanoma.

583 In Trial 1, patients were not permitted to have more than one prior chemotherapy regimen for
584 advanced or metastatic disease; prior treatment with a BRAF inhibitor or MEK inhibitor was not
585 permitted. The primary efficacy outcome measure was progression-free survival (PFS). Patients
586 were randomized to receive MEKINIST 2 mg orally once daily (N = 214) or chemotherapy
587 (N = 108) consisting of either dacarbazine 1,000 mg/m² intravenously every 3 weeks or
588 paclitaxel 175 mg/m² intravenously every 3 weeks. Treatment continued until disease
589 progression or unacceptable toxicity. Randomization was stratified according to prior use of
590 chemotherapy for advanced or metastatic disease (yes versus no) and lactate dehydrogenase level
591 (normal versus greater than upper limit of normal). Tumor tissue was evaluated for BRAF
592 mutations at a central testing site using a clinical trial assay. Tumor samples from 289 patients
593 (196 patients treated with MEKINIST and 93 chemotherapy-treated patients) were also tested
594 retrospectively using an FDA-approved companion diagnostic test, THxID™-BRAF assay.

595 The median age for randomized patients was 54 years, 54% were male, greater than 99% were
596 White, and all patients had baseline ECOG performance status of 0 or 1. Most patients had
597 metastatic disease (94%), were Stage M1c (64%), had elevated LDH (36%), had no history of
598 brain metastasis (97%), and received no prior chemotherapy for advanced or metastatic disease
599 (66%). The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or
600 both (less than 1%). The median durations of follow-up prior to initiation of alternative treatment
601 were 4.9 months for patients treated with MEKINIST and 3.1 months for patients treated with

602 chemotherapy. Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of
603 disease progression to receive MEKINIST.

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

606

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

Investigator-Assessed Endpoints	MEKINIST N = 214	Chemotherapy N = 108
Progression-Free Survival		
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)

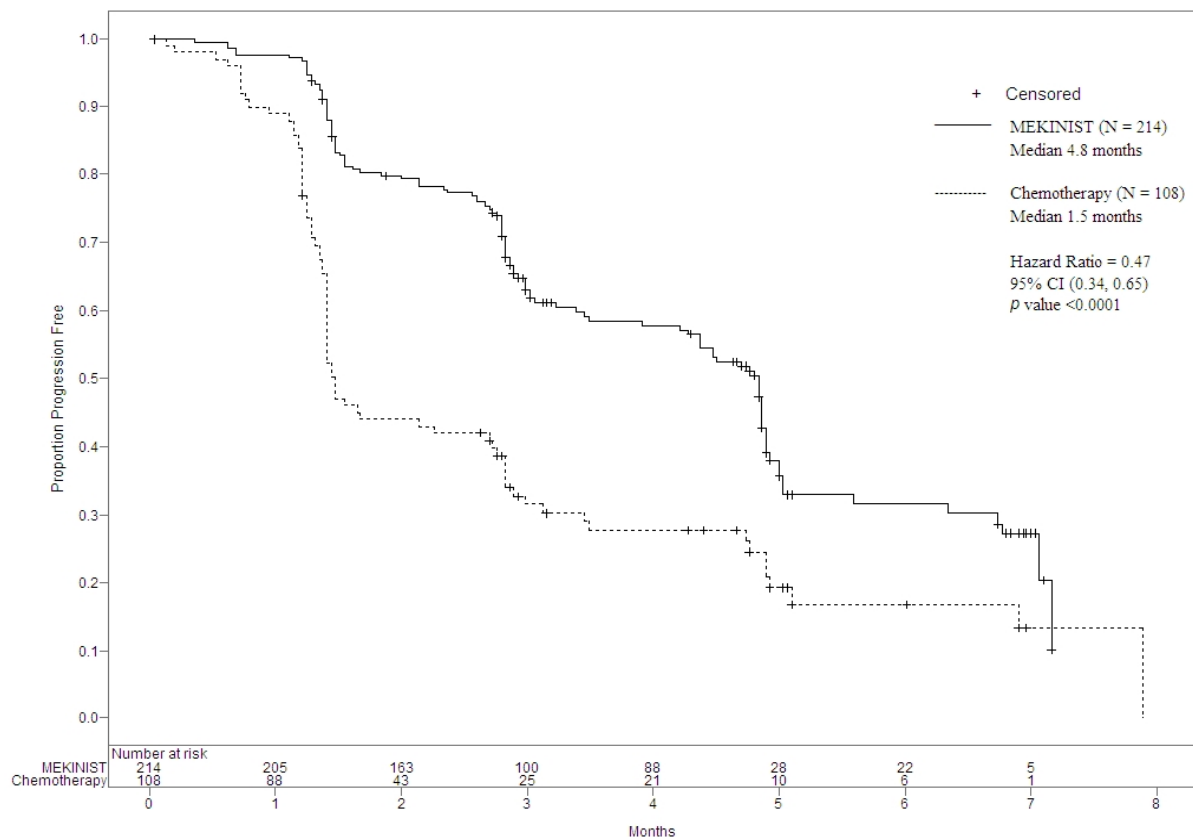
609 CI = Confidence interval; HR = Hazard ratio; CR = Complete response; PR = Partial response;

610 NR = Not reached.

611 ^a Pike estimator.

612

613 **Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival (ITT**
614 **Population) in Trial 1**



615

616 In supportive analyses based on independent radiologic review committee (IRRC) assessment,
617 the PFS results were consistent with those of the primary efficacy analysis.

618 Mekinist with Dabrafenib

619 The safety and efficacy of MEKINIST administered with dabrafenib were evaluated in an
620 international, randomized, double-blind, active-controlled trial (Trial 2). Trial 2 compared
621 dabrafenib plus MEKINIST to dabrafenib plus placebo as first-line treatment for patients with
622 unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive
623 cutaneous melanoma. Patients were randomized (1:1) to receive MEKINIST 2 mg once daily
624 plus dabrafenib 150 mg twice daily or dabrafenib 150 mg twice daily plus matching placebo.
625 Randomization was stratified by lactate dehydrogenase (LDH) level (greater than the upper limit
626 of normal (ULN) vs. \leq ULN) and BRAF mutation subtype (V600E vs. V600K). The major
627 efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1
628 with additional efficacy outcome measures of overall survival (OS) and confirmed overall
629 response rate (ORR).

630

631 In Trial 2, 423 patients were randomized to MEKINIST plus dabrafenib (n = 211) or dabrafenib
632 plus placebo (n = 212). The median age was 56 years (range: 22 to 89 years), 53% were male,
633 >99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIc, 66% had M1c
634 disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients
635 had tumor containing BRAF V600E or V600K mutations as determined by centralized testing
636 with the FDA-approved companion diagnostic test; 85% had BRAF V600E mutation-positive
637 melanoma and 15% had BRAF V600K mutation-positive melanoma.

638 Trial 2 demonstrated statistically significant improvements in PFS and OS (see Table 8 and
639 Figure 2).

640 **Table 8. Efficacy Results in Trial 2**

641

Endpoint[†]	MEKINIST plus dabrafenib N=211	Dabrafenib plus Placebo N=212
Progression-Free Survival (PFS)^a		
Number of events (%)	102 (48%)	109 (51%)
Median, months (95% CI)	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)
HR (95% CI)	0.75 (0.57, 0.99)	
<i>P</i> value ^b	0.035	
Overall Survival		
Number of deaths (%)	99 (47%)	123 (58%)
Median, months (95% CI)	25.1 (19.2, NR)	18.7 (15.2, 23.1)
HR (95% CI)	0.71 (0.55, 0.92)	
<i>P</i> value ^b	0.01	
Overall Response Rate (ORR)^b		
ORR, % (95% CI)	66 (60, 73)	51 (44, 58)
<i>P</i> value	<0.001	
CR, %	10	8
PR, %	56	42
Median duration of response, months (95% CI)	9.2 (7.4, NR)	10.2 (7.5, NR)

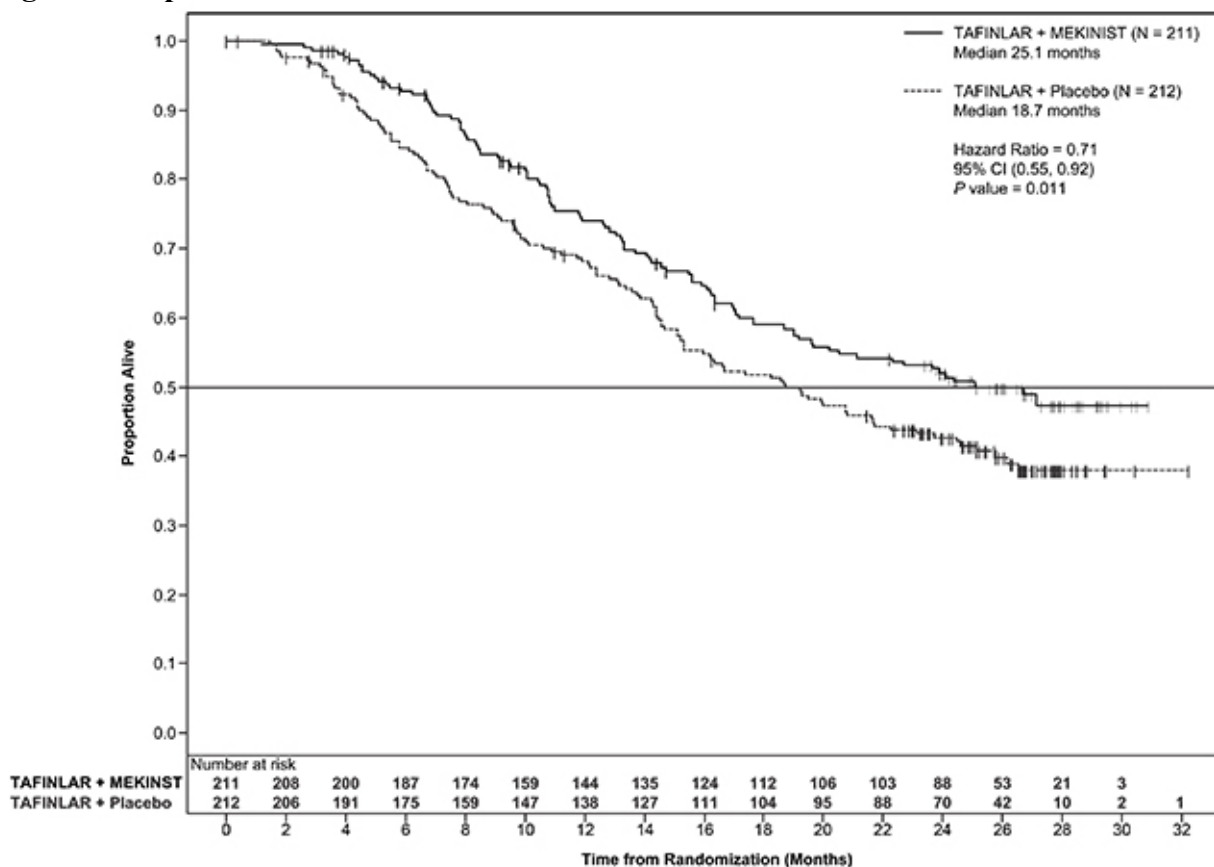
642 [†] CI = Confidence interval; HR = Hazard ratio; CR = Complete response; PR = Partial
643 response; NR = Not reached.

644 ^a PFS and ORR were assessed by investigator.

645 ^b Based on stratified log-rank test

646

647 **Figure 2. Kaplan Meier Curves of Overall Survival in Trial 2**



648
649

650 **14.2 Lack of Clinical Activity in Metastatic Melanoma Following BRAF-Inhibitor**
 651 **Therapy**

652 The clinical activity of MEKINIST as a single agent was evaluated in a single-arm, multicenter,
 653 international trial in 40 patients with BRAF V600E or V600K mutation-positive, unresectable or
 654 metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients
 655 received MEKINIST at a dose of 2 mg orally once daily until disease progression or
 656 unacceptable toxicity.

657 The median age was 58 years, 63% were male, all were White, 98% had baseline ECOG PS of 0
 658 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the
 659 remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No
 660 patient achieved a confirmed partial or complete response as determined by the clinical
 661 investigators.

662 **16 HOW SUPPLIED/STORAGE AND HANDLING**

663 0.5 mg tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one
 664 face and ‘TFC’ on the opposing face and are available in bottles of 30 (NDC 0173-0849-13).

665 2 mg tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and
666 ‘HMJ’ on the opposing face and are available in bottles of 30 (NDC 0173-0848-13).

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

669 **17 PATIENT COUNSELING INFORMATION**

670 Advise the patient to read the FDA-approved patient labeling (Patient Information).

671 Inform patients of the following:

672 Confirmation of BRAF V600E or V600K mutation

673 Evidence of BRAF V600E or V600K mutation within the tumor specimen is necessary to
674 identify patients for whom treatment with MEKINIST is indicated [*see Dosage and*
675 *Administration (2.1)*].

676 New cutaneous and non-cutaneous malignancies

677 MEKINIST administered with dabrafenib can result in the development of new primary
678 cutaneous and non-cutaneous malignancies. Advise patients to contact their doctor immediately
679 for any new lesions, changes to existing lesions on their skin, or other signs and symptoms of
680 malignancies [*see Warnings and Precautions (5.1)*].

681 Hemorrhage

682 MEKINIST administered with dabrafenib increases the risk of intracranial and gastrointestinal
683 hemorrhage. Advise patients to contact their healthcare provider to seek immediate medical
684 attention for signs or symptoms of unusual bleeding or hemorrhage [*see Warnings and*
685 *Precautions (5.2)*].

686 Venous thrombosis

687 MEKINIST administered with dabrafenib increases the risks of pulmonary embolism and deep
688 venous thrombosis. Advise patients to seek immediate medical attention for sudden onset of
689 difficulty breathing, leg pain, or swelling [*see Warnings and Precautions (5.3)*].

690 Cardiomyopathy

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

693 Retinal Pigment Epithelial Detachment

694 MEKINIST can cause severe visual disturbances that can lead to blindness. Advise patients to
695 contact their healthcare provider if they experience any changes in their vision [*see Warnings*
696 *and Precautions (5.5)*].

697 Interstitial lung disease

698 MEKINIST can cause interstitial lung disease (or pneumonitis). Advise patients to contact their
699 healthcare provider as soon as possible if they experience signs such as cough or dyspnea [*see*
700 *Warnings and Precautions (5.6)*].

701 Serious febrile reactions

702 MEKINIST administered with dabrafenib can cause serious febrile reactions. Instruct patients to
703 contact their healthcare provider if they develop fever while taking MEKINIST with dabrafenib
704 [*see Warnings and Precautions (5.7)*].

705 Serious skin toxicities

706 MEKINIST can cause serious skin toxicities which may require hospitalization. Advise patients
707 to contact their healthcare provider for progressive or intolerable rash [*see Warnings and*
708 *Precautions (5.8)*].

709 Hypertension

710 MEKINIST can cause hypertension. Advise patients that they need to undergo blood pressure
711 monitoring and to contact their healthcare provider if they develop symptoms of hypertension
712 such as severe headache, blurry vision, or dizziness.

713 Diarrhea

714 MEKINIST often causes diarrhea which may be severe in some cases. Inform patients of the
715 need to contact their healthcare provider if severe diarrhea occurs during treatment.

716 Embryo-fetal Toxicity

717 MEKINIST can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the
718 potential risk to a fetus [*see Warnings and Precautions (5.10), Use in Specific Populations (8.1,*
719 *8.3)*].

720 Females and males of reproductive potential

721 Instruct females of reproductive potential to use highly effective contraception during treatment
722 with MEKINIST and for 4 months after the last dose. Advise patients to contact their healthcare
723 provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST [*see*
724 *Warnings and Precautions (5.10), Use in Specific Populations (8.1, 8.3)*].

725 Lactation

726 Advise women not to breastfeed during treatment with MEKINIST and for 4 months after the
727 last dose [*see Use in Specific Populations (8.2)*].

728 Infertility

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

731 Instructions for taking MEKINIST

732 MEKINIST should be taken at least 1 hour before or at least 2 hours after a meal [*see Dosage*
733 *and Administration (2.2)*].

734

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736 THxID BRAF[™] assay is a trademark of bioMérieux.

737



738

739 GlaxoSmithKline

740 Research Triangle Park, NC 27709

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742 MKN:3PI

743

<p style="text-align: center;">Patient Information MEKINIST® (MEK-in-ist) (trametinib) tablets</p>
<p>If your healthcare provider prescribes MEKINIST for you to be taken with dabrafenib, also read the Medication Guide that comes with dabrafenib.</p>
<p>What is the most important information I should know about MEKINIST? MEKINIST, when used with dabrafenib, may cause:</p> <ul style="list-style-type: none">• a type of skin cancer, called cutaneous squamous cell carcinoma (cuSCC)• new cancers including basal cell carcinoma. <p>Talk to your healthcare provider about your risk for these cancers. Check your skin and tell your healthcare provider right away about any skin changes including a:</p> <ul style="list-style-type: none">• new wart• skin sore or reddish bump that bleeds or does not heal• change in size or color of a mole <p>Your healthcare provider should check your skin before treatment with MEKINIST and dabrafenib, every two months during treatment with MEKINIST and dabrafenib and for up to 6 months after you stop taking MEKINIST and dabrafenib to look for any new skin cancers.</p> <p>Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that develop during treatment with MEKINIST with dabrafenib.</p> <p>See "What are the possible side effects of MEKINIST?" for more information about side effects.</p>
<p>What is MEKINIST?</p> <p>MEKINIST is a prescription medicine used by itself or with a medicine called dabrafenib, to treat people with a type of skin cancer called melanoma:</p> <ul style="list-style-type: none">• 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. <p>Your healthcare provider will perform a test to make sure that MEKINIST is right for you.</p> <p>MEKINIST should not be used to treat people who already have received a BRAF inhibitor for treatment of their melanoma.</p> <p>It is not known if MEKINIST alone or MEKINIST with dabrafenib is safe and effective in children.</p>
<p>What should I tell my healthcare provider before taking MEKINIST?</p> <p>Before you take MEKINIST, tell your healthcare provider if you:</p> <ul style="list-style-type: none">• have had bleeding problems or blood clots• have heart problems• have eye problems• have lung or breathing problems• have high blood pressure (hypertension)• have liver or kidney problems• have any other medical conditions

- are pregnant or plan to become pregnant. MEKINIST can harm your unborn baby.
 - Females who are able to become pregnant should use effective birth control (contraception) during treatment with MEKINIST and for 4 months after your last dose of MEKINIST.
 - Talk to your healthcare provider about birth control methods that may be right for you during this time.
 - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with MEKINIST.
- are breastfeeding or plan to breastfeed. It is not known if MEKINIST passes into your breast milk.
 - Do not breastfeed during treatment and for 4 months after your last dose of MEKINIST. Talk to your healthcare provider about the best way to feed your baby during this time.

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

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

How should I take MEKINIST?

- Take MEKINIST exactly as your healthcare provider tells you to take it. Do not change your dose or stop MEKINIST unless your healthcare provider tells you.
- Take MEKINIST one time a day, at the same time each day.
- Take MEKINIST at least 1 hour before or 2 hours after a meal.
- If you miss a dose, take it as soon as you remember. If it is less than 12 hours before your next scheduled dose, skip the missed dose. Just take the next dose at your regular time.

What are the possible side effects of MEKINIST?

MEKINIST may cause serious side effects, including:

- **See “What is the most important information I should know about MEKINIST?”**
- **bleeding problems.** MEKINIST can cause serious bleeding problems, especially in your brain or stomach, and can lead to death. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
 - headaches, dizziness, or feeling weak
 - cough up blood or blood clots
 - vomit blood or your vomit looks like “coffee grounds”
 - red or black stools that look like tar
- **blood clots.** MEKINIST can cause blood clots in your arms or legs, which can travel to your lungs and can lead to death. Get medical help right away if you have the following symptoms:
 - chest pain
 - sudden shortness of breath or trouble breathing
 - pain in your legs with or without swelling
 - swelling in your arms or legs
 - a cool pale arm or leg
- **heart problems**, including heart failure. Your healthcare provider should check your heart function before and during treatment with MEKINIST. Call your healthcare provider right away if you have any

of the following signs and symptoms of a heart problem:

- feeling like your heart is pounding or racing
- shortness of breath
- swelling of your ankles and feet
- feeling lightheaded
- **eye problems.** MEKINIST can cause severe eye problems that might lead to blindness. Call your healthcare provider right away if you get these symptoms of eye problems:
 - blurred vision, loss of vision, or other vision changes
 - see color dots
 - halo (seeing blurred outline around objects)
 - eye pain, swelling, or redness
- **lung or breathing problems.** MEKINIST can cause lung or breathing problems. Tell your healthcare provider if you have any new or worsening symptoms of lung or breathing problems, including:
 - shortness of breath
 - cough
- **fever.** Fever is common during treatment with MEKINIST and dabrafenib, but it may also be serious. When taking MEKINIST with dabrafenib, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. Call your healthcare provider right away if you get a fever during treatment with MEKINIST.
- **skin reactions.** Rash is a common side effect of MEKINIST. MEKINIST can also cause other skin reactions. In some cases these rashes and other skin reactions can be severe, and may need to be treated in a hospital. Call your healthcare provider if you get any of the following symptoms:
 - skin rash that bother you or does not go away
 - acne
 - redness, swelling, peeling, or tenderness of hands or feet
 - skin redness
- **increased blood sugar (hyperglycemia).** Some people may develop high blood sugar or worsening diabetes during treatment with MEKINIST and dabrafenib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with MEKINIST and dabrafenib. Your diabetes medicine may need to be changed. Tell your healthcare provider if you have any of the following symptoms of severe high blood sugar:
 - increased thirst
 - urinating more often than normal or urinating an increased amount of urine

The most common side effects of MEKINIST when taken alone include:

- diarrhea. Call your healthcare provider if you get severe diarrhea.
- swelling of the face, arms, or legs

Common side effects of MEKINIST when taken with dabrafenib include:

- nausea
- vomiting
- chills
- high blood pressure (hypertension)

- diarrhea
- swelling of the face, arms, or legs

MEKINIST can cause new or worsening high blood pressure (hypertension). Your healthcare provider should check your blood pressure during treatment with MEKINIST. Call your healthcare provider right away if you develop high blood pressure, your blood pressure worsens, or you have severe headache, lightheadedness, or dizziness.

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

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of MEKINIST. For more information, ask your healthcare provider or pharmacist.

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

How should I store MEKINIST?

- Store MEKINIST in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not freeze.
- Keep MEKINIST dry and away from moisture and light.
- The bottle of MEKINIST contains a desiccant packet to help keep your medicine dry. Do not throw away the desiccant packet.
- Keep MEKINIST in its original bottle. Do not place tablets in a pill box.
- Safely throw away MEKINIST that is out of date or no longer needed.

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

General information about the safe and effective use of MEKINIST.

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

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

What are the ingredients in MEKINIST?

Active ingredient: trametinib

Inactive ingredients:

Tablet Core: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate (vegetable source), mannitol, microcrystalline cellulose, sodium lauryl sulfate.

Tablet Coating: hypromellose, iron oxide red (2 mg tablets), iron oxide yellow (0.5 mg tablets), polyethylene glycol, polysorbate 80 (2 mg tablets), titanium dioxide.



GlaxoSmithKline
Research Triangle Park, NC 27709

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