

## 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](http://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<sup>®</sup> 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**

<b>Dose Reductions for MEKINIST</b>	
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**

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

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

31 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)  
 32 version 4.0.

33 <sup>b</sup> 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/m<sup>2</sup> every 3 weeks or paclitaxel 175 mg/m<sup>2</sup> 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 <sup>a</sup>	Grades 3 and 4 <sup>b</sup>	All Grades <sup>a</sup>	Grades 3 and 4 <sup>b</sup>
<b>Skin and subcutaneous tissue disorders</b>				
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
<b>Gastrointestinal disorders</b>				
Diarrhea	43	0	16	2
Stomatitis <sup>c</sup>	15	2	2	0
Abdominal pain <sup>d</sup>	13	1	5	1
<b>Vascular disorders</b>				
Lymphedema <sup>e</sup>	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage <sup>f</sup>	13	<1	0	0

277 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.  
 278 <sup>b</sup> Grade 4 adverse reactions limited to rash (n = 1) in trametinib arm and diarrhea (n = 1) in chemotherapy arm.  
 279 <sup>c</sup> Includes stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.  
 280 <sup>d</sup> Includes abdominal pain, lower abdominal pain, upper abdominal pain, and abdominal tenderness.  
 281 <sup>e</sup> Includes lymphedema, edema, and peripheral edema.  
 282 <sup>f</sup> Includes epistaxis, gingival bleeding, hematochezia, 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)<sup>a</sup>**

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 <sup>a</sup> 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  $\geq 480$  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<sup>a</sup>**

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 (%)
<b>General disorders and administrative site conditions</b>						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Edema peripheral <sup>b</sup>	21	0.7	25	1.4	11	0.5
<b>Gastrointestinal disorders</b>						
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 <sup>c</sup>	18	0.9	26	1.0	14	2.4
<b>Nervous system disorders</b>						
Dizziness	11	0.2	14	0	7	0
<b>Vascular disorders</b>						
Hypertension	26	11	25	6	16	6
Hemorrhage <sup>d</sup>	18	2.0	19	1.9	15	1.9
<b>Skin and subcutaneous tissue disorders</b>						
Rash <sup>e</sup>	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 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

341 <sup>b</sup> Includes peripheral edema, edema, lymphedema, localized edema, and generalized edema.

342 <sup>c</sup> Includes abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal discomfort.

343 <sup>d</sup> 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 <sup>e</sup> 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 <sup>a</sup>		Trial 2			
			MEKINIST plus Dabrafenib N = 209 <sup>b</sup>		Dabrafenib N = 211 <sup>b</sup>	
	All Grades (%)	Grades 3 and 4 <sup>c</sup> (%)	All Grades (%)	Grades 3 and 4 <sup>c</sup> (%)	All Grades (%)	Grades 3 and 4 <sup>c</sup> (%)
<b>Hematology</b>						
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
<b>Liver Function Tests</b>						
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
<b>Chemistry</b>						
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 <sup>a</sup> For these laboratory tests the denominator is 556.

361 <sup>b</sup> For these laboratory tests the denominator is 208 for the combination arm, 207-209 for the dabrafenib arm.

362 <sup>c</sup> 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.

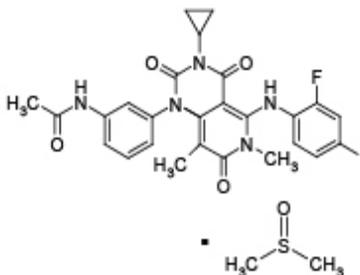
## 445 **10 OVERDOSAGE**

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 trioxopyrido[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 m<sup>2</sup>) and 35 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m<sup>2</sup>), 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  $\mu$ 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<sub>max</sub> 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  $\mu$ 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  $\geq 0.016$  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/m<sup>2</sup> intravenously every 3 weeks or  
588 paclitaxel 175 mg/m<sup>2</sup> 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**

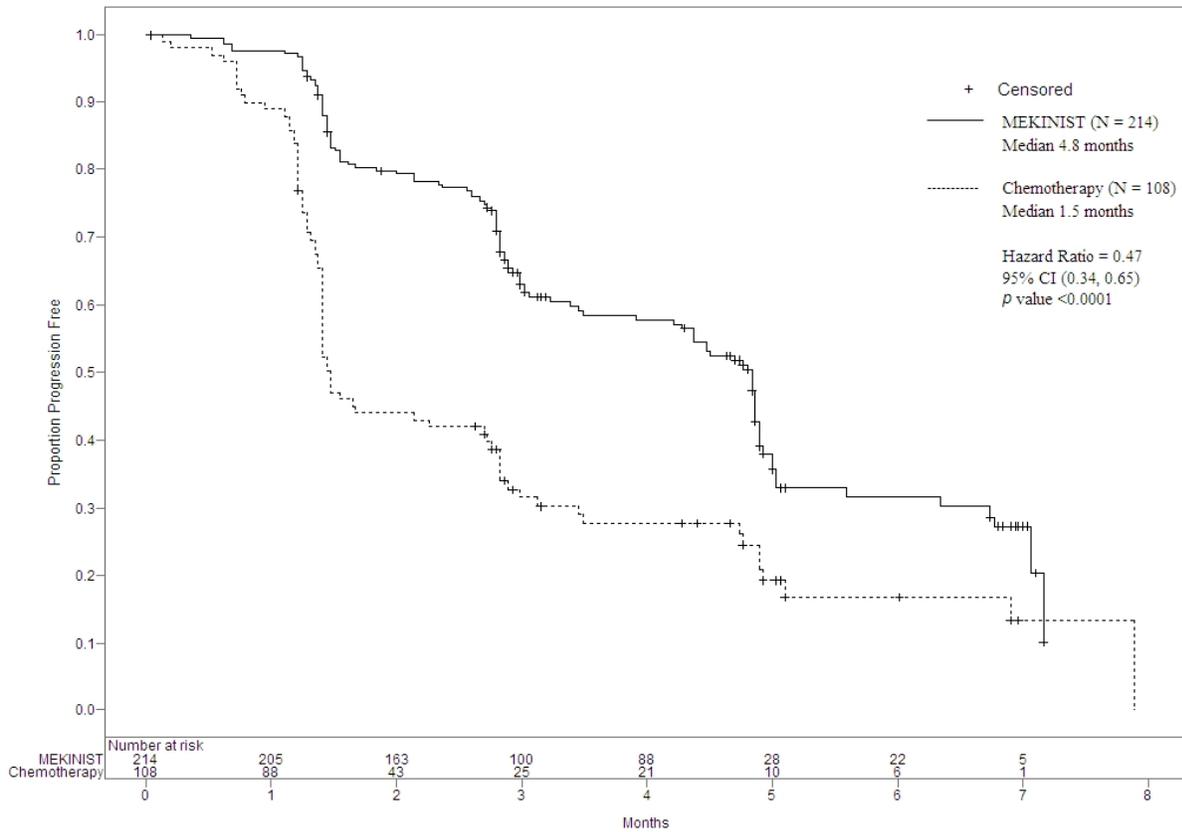
<b>Investigator-Assessed Endpoints</b>	<b>MEKINIST N = 214</b>	<b>Chemotherapy N = 108</b>
<b>Progression-Free Survival</b>		
Number of Events (%)	117 (55%)	77 (71%)
Progressive Disease	107 (50%)	70 (65%)
Death	10 (5%)	7 (6%)
Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR <sup>a</sup> (95% CI)	0.47 (0.34, 0.65)	
<i>P</i> value (log-rank test)	<i>P</i> <0.0001	
<b>Confirmed Tumor Responses</b>		
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 <sup>a</sup> 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

<b>Endpoint<sup>†</sup></b>	<b>MEKINIST plus dabrafenib N=211</b>	<b>Dabrafenib plus Placebo N=212</b>
<b>Progression-Free Survival (PFS)<sup>a</sup></b>		
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 <sup>b</sup>	0.035	
<b>Overall Survival</b>		
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 <sup>b</sup>	0.01	
<b>Overall Response Rate (ORR)<sup>b</sup></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)

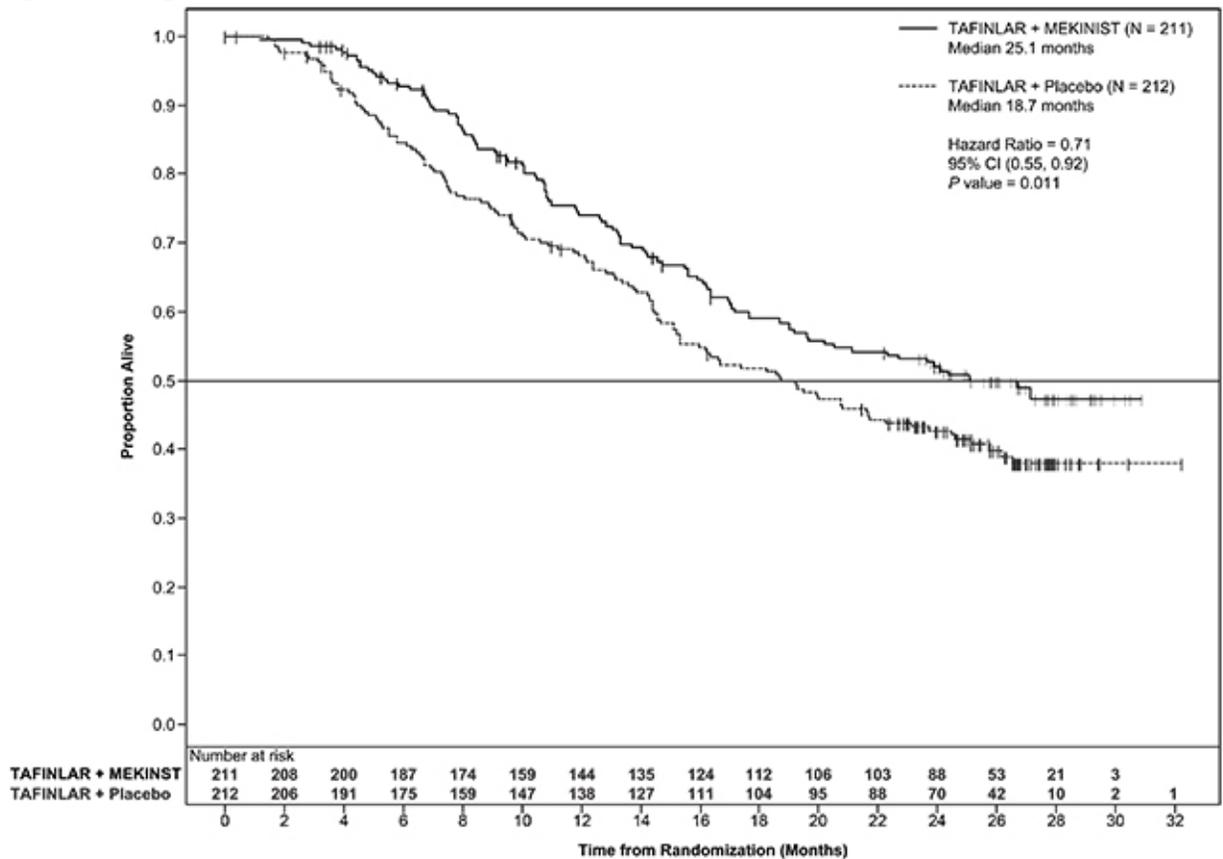
642 <sup>†</sup> CI = Confidence interval; HR = Hazard ratio; CR = Complete response; PR = Partial  
643 response; NR = Not reached.

644 <sup>a</sup> PFS and ORR were assessed by investigator.

645 <sup>b</sup> 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

735 MEKINIST is a registered trademark of the GSK group of companies.

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

**Patient Information**  
MEKINIST® (MEK-in-ist)  
(trametinib)  
tablets

If your healthcare provider prescribes MEKINIST for you to be taken with dabrafenib, also read the Medication Guide that comes with dabrafenib.

**What is the most important information I should know about MEKINIST?**

**MEKINIST, when used with dabrafenib, may cause:**

- a type of skin cancer, called cutaneous squamous cell carcinoma (cuSCC)
- new cancers including basal cell carcinoma.

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:

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

Your healthcare provider should check your skin before treatment with 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.

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.

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

**What is MEKINIST?**

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:

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

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

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

It is not known if MEKINIST alone or MEKINIST with dabrafenib is safe and effective in children.

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

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

- 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](http://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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