HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MEKINIST (trametinib) tablets, for oral use
Initial U.S. Approval: 2013

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

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

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

---------- DOSAGE AND ADMINISTRATION ----------

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

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

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

----------CONTRAINDICATIONS----------

None. (4)

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

- Cardiomyopathy: Re-assess LVEF after one month of treatment, and evaluate approximately every 2 to 3 months thereafter. (5.1)
- Retinal Pigment Epithelial Detachment (RPED): Perform ophthalmologic evaluation for any visual disturbances. Withhold MEKINIST if RPED is diagnosed and discontinue if no improvement after 3 weeks. (5.2)
- Retinal Vein Occlusion (RVO): Discontinue MEKINIST. (5.3)
- Interstitial Lung Disease (ILD): Withhold MEKINIST for new or progressive unexplained pulmonary symptoms or findings, such as cough, dyspnea, hypoxia, or infiltrates. Permanently discontinue MEKINIST for treatment-related ILD or pneumonitis. (5.4)
- Serious Skin Toxicity: Monitor for skin toxicities and for secondary infections. Discontinue for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of MEKINIST. (5.5)
- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus. (5.6, 8.1, 8.6)

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

Most common adverse reactions (≥20%) for MEKINIST include rash, diarrhea, and lymphedema. (6.1)

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

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

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

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

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

2.2 Recommended Dosing

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

2.3 Dose Modifications

Table 1. Recommended Dose Modifications for MEKINIST

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

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

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

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

5.2 Retinal Pigment Epithelial Detachment (RPED)

Retinal pigment epithelial detachments (RPED) can occur during treatment with MEKINIST. In Trial 1, where ophthalmologic examinations including retinal evaluation were performed pretreatment and at regular intervals during treatment, one patient (0.5%) receiving MEKINIST developed RPED and no cases of RPED were identified in chemotherapy-treated patients. Across all clinical trials of MEKINIST, the incidence of RPED was 0.8% (14/1749).

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

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

5.3 Retinal Vein Occlusion (RVO)

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

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

5.4 Interstitial Lung Disease

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

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

5.5 Serious Skin Toxicity

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

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

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

5.6 Embryofetal Toxicity

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

Table 2. Selected Adverse Reactions Occurring in ≥10% of Patients Receiving MEKINIST and at a Higher Incidence than in the Control Arm[a]

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

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

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

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

Nervous System Disorders: Dizziness, dysgeusia.

Ocular Disorders: Vision blurred, dry eye.

Infections and Infestations: Folliculitis, rash pustular, cellulitis.

Cardiac Disorders: Bradycardia.

Gastrointestinal Disorders: Xerostomia.

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis

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

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

[a] No Grade 4 events were reported in either treatment arm.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Females and Males of Reproductive Potential

Contraception: *Females*

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

Infertility: *Females*

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

8.7 Hepatic Impairment

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

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

8.8 Renal Impairment

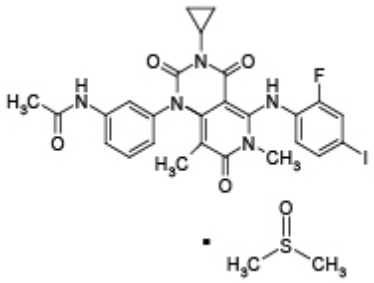
No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild or moderate renal impairment based on a population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. The appropriate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

10 OVERDOSAGE

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

11 DESCRIPTION

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



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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

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

Metabolism: Trametinib is metabolized predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways in vitro. Deacetylation is likely mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases.

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

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

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

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

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

Renal Impairment: As renal excretion of trametinib is low (<20%), renal impairment is unlikely to have a clinically important effect on the exposure of trametinib. Based on a population PK analysis in 223 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 m^2) and 35 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m^2), mild and moderate renal impairment have no clinically important effects on the systemic exposure of trametinib. The PK of trametinib have not been studied in patients with severe renal impairment *[see Use in Specific Populations (8.8)]*.

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

14.1 BRAF V600E or V600K Mutation-Positive Metastatic Melanoma

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

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

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

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

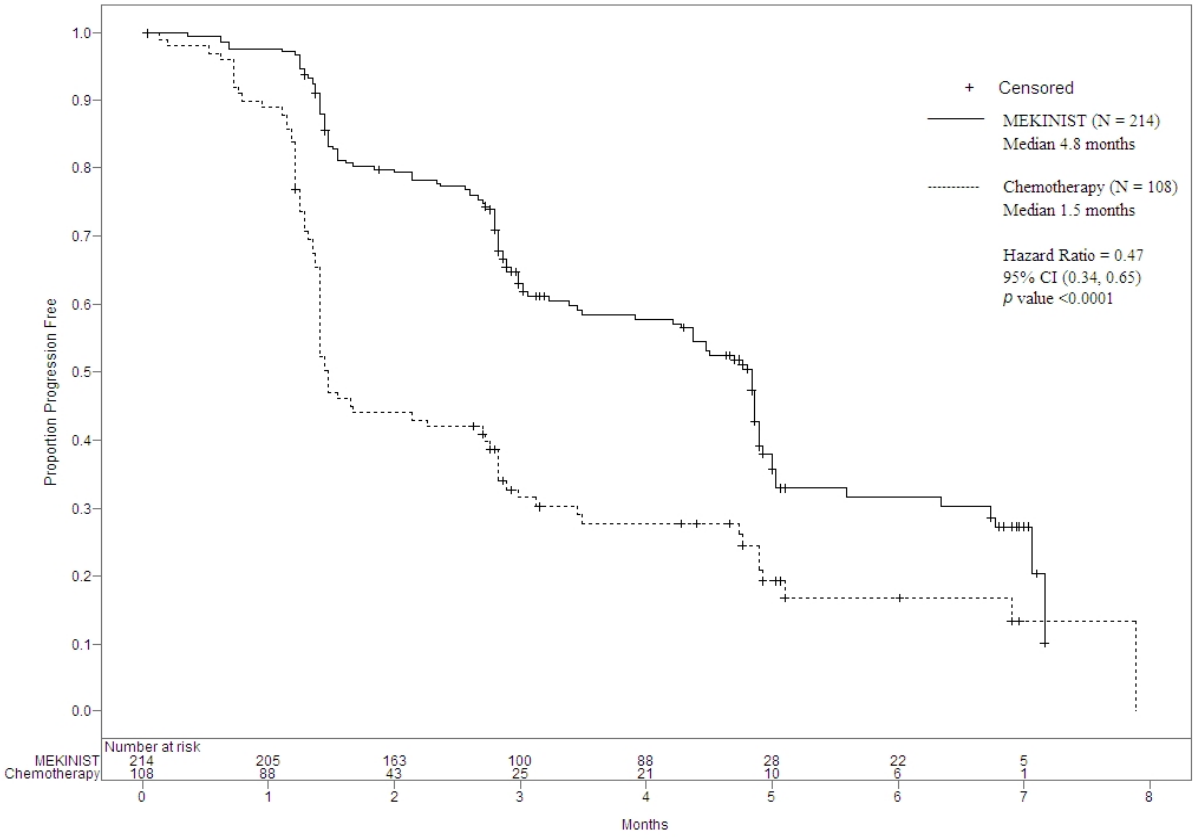
Table 4. Investigator-Assessed Progression-Free Survival and Confirmed Objective Response Results

	MEKINIST N = 214	Chemotherapy N = 108
PFS		
Number of Events (%)	117 (55%)	77 (71%)
Progressive Disease	107 (50%)	70 (65%)
Death	10 (5%)	7 (6%)
Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR[a] (95% CI)	0.47 (0.34, 0.65)	
P value (log-rank test)	*P*<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)

[a] Pike estimator.

CI = confidence interval; CR=complete response; HR = Hazard Ratio; NR=Not reached, PFS = Progression-free Survival; PR=partial response.

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



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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Inform patients of the following:

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

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

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THxID BRAF™ assay is a trademark of bioMerieux.

GlaxoSmithKline

Research Triangle Park, NC 27709

MKN:1PI

Patient Information

MEKINIST™ (MEK-in-ist)
(trametinib)
tablets

What is MEKINIST?

MEKINIST is a prescription medicine used 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

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

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

It is not known if MEKINIST 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 heart problems
- have lung or breathing problems
- have eye 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.
    - Women who may become pregnant should use effective birth control (contraception) during treatment with MEKINIST and for 4 months after stopping treatment. Talk to your healthcare provider about birth control methods that may be right for you. Tell your healthcare provider right away if you become pregnant during treatment with MEKINIST.
- are breastfeeding or plan to breastfeed. It is not known if MEKINIST passes into your breast milk. You and your healthcare provider should decide if you will take MEKINIST or breastfeed. You should not do both.

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.
- Take MEKINIST 1 hour before or 2 hours after meals.
- If you miss a dose, take it as soon as you remember. If it is within 12 hours of your next scheduled dose, skip the missed dose. Just take the next dose at your regular time.
- If you take too much MEKINIST, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of MEKINIST?

MEKINIST may cause serious side effects, including:

- **heart problems, including heart failure.** Your healthcare provider should check your heart function before you start taking MEKINIST and during treatment. Signs and symptoms of heart problems may include:
    - feeling like your heart is pounding or racing
    - shortness of breath
    - swelling of your ankles and feet
    - feeling lightheaded
- **eye problems.** MEKINIST can cause eye problems including blindness. Tell 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)
- **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
- **skin rash.** Rash is the most common side effect of MEKINIST and in some cases can be severe and can result in admission to the hospital if severe. Tell your healthcare provider if you get any of the following symptoms:
    - skin rash
    - acne
    - redness, swelling, peeling, or tenderness of hands or feet

- skin redness

The most common side effects of MEKINIST include:

- 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. Tell your healthcare provider if you develop high blood pressure, your blood pressure worsens, or you have severe headache, lightheadedness, or dizziness.

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

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

MEKINIST is a trademark of GlaxoSmithKline.

GlaxoSmithKline

Research Triangle Park, NC 27709

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